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FILE 'REGISTRY' ENTERED AT 13:54:52 ON 08 DEC 2004
E ANTI-CD22/CN
E ANTI CD22/CN

FILE 'HCAPLUS' ENTERED AT 13:55:26 ON 08 DEC 2004
L1 43 SEA ABB=ON ?ANTI?(W)?CD22?(W)?ANTIBOD?
L2 37 SEA ABB=ON L1 AND (?HUMAN? OR ?CHIMER?)

FILE 'REGISTRY' ENTERED AT 13:57:21 ON 08 DEC 2004
L3 1 SEA ABB=ON BORON/CN

FILE 'HCAPLUS' ENTERED AT 13:57:32 ON 08 DEC 2004
L4 21 SEA ABB=ON L2 AND (L3 OR ?DRUG? OR ?TOXIN? OR ?IMMUNOMODULAT?
OR ?CHELAT? OR ?BORON? OR ?PHOTOACT?(W)(?AGENT? OR DYE?) OR
?RADIOISOTOP?)

FILE 'REGISTRY' ENTERED AT 13:58:42 ON 08 DEC 2004
L5 0 SEA ABB=ON L4 AND ?IODIN?
L6 1 SEA ABB=ON IODINE/CN

FILE 'HCAPLUS' ENTERED AT 13:59:32 ON 08 DEC 2004
L7 3 SEA ABB=ON L4 AND (L6 OR ?IODIN?)
L8 21 SEA ABB=ON L4 OR L7

FILE 'REGISTRY' ENTERED AT 13:59:58 ON 08 DEC 2004
L9 12 SEA ABB=ON (CYCLOPHOSPHAMIDE OR ETOPOSIDE OR VINCRISTINE OR
PROCARBAZINE OR PREDNISONE OR CARMUSTINE OR DOXORUBICIN OR
METHOTREXATE OR BLEOMYCIN OR DEXAMETHASONE OR PHENYL BUTYRATE
OR BRYOSTATIN-1 OR LEUCOVORIN)/CN
E BRYOSTATIN/CN

L10 1 SEA ABB=ON "BRYOSTATIN 1"/CN
L11 13 SEA ABB=ON L9 OR L10

FILE 'HCAPLUS' ENTERED AT 14:01:18 ON 08 DEC 2004
L12 6 SEA ABB=ON L8 AND (CYCLOPHOSPHAMIDE OR ETOPOSIDE OR VINCRISTIN
E OR PROCARBAZINE OR PREDNISONE OR CARMUSTINE OR DOXORUBICIN
OR METHOTREXATE OR BLEOMYCIN OR DEXAMETHASONE OR PHENYL
BUTYRATE OR BRYOSTATIN-1 OR LEUCOVORIN)

FILE 'REGISTRY' ENTERED AT 14:01:42 ON 08 DEC 2004
L13 2 SEA ABB=ON (NITROGEN MUSTARD OR NITROSOUreas OR TRIAZENES OR
FOLIC ACID ANALOGS OR PYRIMIDINE ANALOGS OR PURINE ANALOGS OR
EPIPODOPHYLLOTOXINS OR PLATINUM OR HORMONES)/CN

FILE 'HCAPLUS' ENTERED AT 14:03:53 ON 08 DEC 2004
L14 3 SEA ABB=ON L8 AND (L13 OR NITROGEN MUSTARD OR NITROSOUreas OR
TRIAZENES OR FOLIC ACID ANALOGS OR PYRIMIDINE ANALOGS OR
PURINE ANALOGS OR EPIPODOPHYLLOTOXINS OR PLATINUM(W)?COORD?(W)?
COMPOUND? OR HORMONES)

FILE 'REGISTRY' ENTERED AT 14:04:32 ON 08 DEC 2004
L15 4 SEA ABB=ON (RICIN OR ABRIN OR RIBONUCLEASE OR DNASE 1 OR
STAPHYLOCOCCAL ENTEROTOXIN-A OR POKEWEED ANTIVIRAL PROTEIN OR
GELONIN OR DIPHTHERIN TOXIN OR PSEUDOMONAS EXOTOXIN OR
PSEUDOMONAS ENDOTOXIN)/CN
E DNASE-1/CN

FILE 'HCAPLUS' ENTERED AT 14:05:38 ON 08 DEC 2004

L16 13 SEA ABB=ON L8 AND (L15 OR RICIN OR ABRIN OR RIBONUCLEASE OR DNASE 1 OR STAPHYLOCOCCAL ENTEROTOXIN-A OR POKEWEED ANTIVIRAL PROTEIN OR GELONIN OR DIPHTHERIN TOXIN OR PSEUDOMONAS EXOTOXIN OR PSEUDOMONAS ENDOTOXIN)

L17 21 SEA ABB=ON L4 OR L12 OR L14 OR L16

FILE 'REGISTRY' ENTERED AT 14:12:19 ON 08 DEC 2004

L18 3 SEA ABB=ON (G-CSF OR GM-CSF OR THROMBOPOIETIN OR IL-1 OR IL-3 OR IL-12)/CN
 E IL 1/CN
 E IL 3/CN
 E IL 12/CN

FILE 'HCAPLUS' ENTERED AT 14:13:27 ON 08 DEC 2004

L19 5 SEA ABB=ON L17 AND (L18 OR IL 1 OR IL 2 OR IL 12)

FILE 'REGISTRY' ENTERED AT 14:15:05 ON 08 DEC 2004

L20 3 SEA ABB=ON (CD 9 OR CD 20 OR CD 52 OR CD 74)/CN

FILE 'HCAPLUS' ENTERED AT 14:16:40 ON 08 DEC 2004

L21 0 SEA ABB=ON L17 AND (L20 OR CD(W) (9 OR 20 OR 52 OR 74))
 0 SEA ABB=ON L17 AND (L20 OR CD 9 OR CD 20 OR CD 52 OR CD 74)
 6 SEA ABB=ON L17 AND (L20 OR CD9 OR CD20 OR CD52 OR CD74)
 0 SEA ABB=ON L21 AND (?QUINTAVAL?(W)?FUSION?(W)?PROTEIN? OR
 ?BLOOD? OR ?LYMPH? OR ?EXTRACELL?(W)?FLUID? OR VH OR VL OR
 ?PEPTID?(W)?LINK? OR FAB OR ?EPITOP?(W)(A OR B OR C OR D OR E)
 OR ?NAKED?)

FILE 'REGISTRY' ENTERED AT 14:21:05 ON 08 DEC 2004

E P-BROMOACETAMIDO-BENZYL-TETRAETHYLAMINETETRAACETIC ACID/CN

FILE 'HCAPLUS' ENTERED AT 14:22:27 ON 08 DEC 2004

L25 6 SEA ABB=ON L17 AND (L19 OR L23 OR P-BROMOACETAMIDO-BENZYL-TETR
 AETHYLAMINETETRACETIC ACID)

L26 21 SEA ABB=ON L17 OR L19 OR L23 OR L25 *21 cits from CA Plus*

FILE 'MEDLINE, BIOSIS, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT 15:05:20 ON
 08 DEC 2004

L27 48 SEA ABB=ON L17

L28 30 DUP REMOV L27 (18 DUPLICATES REMOVED) *30 cits from other
 databases*

antigens on Daudi cells (CD19 and CD22) were stably expressed in all the neoplastic lesions. Radiolabelled anti-**CD22 antibodies** localized in organs infiltrated with tumor, but did not penetrate primary s.c. tumors. This model of disseminated vs. solid tumor should prove useful for evaluating the efficacy of different types and doses of therapeutic antibodies, immunoconjugates and **immunotoxins** prepared from anti-**human** B-cell antibodies.

L28 ANSWER 30 OF 30 MEDLINE on STN DUPLICATE 12
 ACCESSION NUMBER: 89089800 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 2463099
 TITLE: The epitope specificity and tissue reactivity of four murine monoclonal anti-**CD22 antibodies**.
 AUTHOR: Li J L; Shen G L; Ghetie M A; May R D; Till M; Ghetie V;
 Uhr J W; Janossy G; Thorpe P E; Amlot P; +
 CORPORATE SOURCE: Department of Microbiology, University of Texas
 Southwestern Medical Center, Dallas 75235.
 CONTRACT NUMBER: AI-11851 (NIAID)
 CA-28149 (NCI)
 CA-41081 (NCI)
 SOURCE: Cellular immunology, (1989 Jan) 118 (1) 85-99.
 Journal code: 1246405. ISSN: 0008-8749.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 198902
 ENTRY DATE: Entered STN: 19900308
 Last Updated on STN: 19980206
 Entered Medline: 19890216

AB The CD22 antigen is expressed on the surface of normal **human** B cells and some neoplastic B cell lines and tumors. Previous cross-blocking studies using a panel of monoclonal anti-**CD22 antibodies** have defined four epitope groups, termed A-D. In the present studies, we have further dissected the epitopes recognized by four monoclonal anti-**CD22 antibodies** using immunoprecipitation and cross-blocking techniques, immunofluorescence analyses with a variety of cell lines, and immunoperoxidase analyses of 36 normal **human** tissues. Two of the antibodies, HD6 and RFB4, have been described previously, and two, UV22-1 and UV22-2, are described in this report. Our studies indicate that the four monoclonal antibodies show unexpected complexities in their reactivity with CD22+ and CD22- cells and their reactivity with solubilized CD22 molecules. The four antibodies, which recognize epitopes defined previously as CD22-A and CD22-B, further subdivide these epitope clusters into four determinants, A1, A2, B1, and B2. Furthermore, only two of the antibodies, RFB4 and UV22-2, are B cell-specific. In summary, our data indicate that RFB4 and UV22-2 would be the antibodies of choice for constructing **immunotoxins** to treat B cell tumors.

AB Fifteen patients with refractory B-cell lymphoma were treated in a Phase I dose escalation clinical trial with a highly potent **immunotoxin** consisting of the Fab' fragment of a monoclonal **anti-CD22 antibody** (RFB4) coupled to chemically deglycosylated **ricin A chain**. All patients had low, intermediate, or high grade non-Hodgkin's lymphoma. The **immunotoxin** was administered i.v. in two to six doses at 48-h intervals. The peak serum concentration and the t_{1/2} were not dose dependent among patients and averaged 1.3 micrograms/ml and .86 min, respectively. Three patients made antibody against A chain, and a fourth made antibody against both A chain and mouse immunoglobulin. Antibody responses were low (less than or equal to 85 micrograms/ml) in three patients and were not detected until 1 mo after treatment. The maximum tolerated dose of the **immunotoxin** was 75 mg/m². Dose-related toxicities included vascular leak syndrome, fever, anorexia, and myalgia. Dose-limiting toxicities included pulmonary edema and/or effusion, expressive aphasia, and rhabdomyolysis (resulting in reversible kidney failure). There was no evidence of liver dysfunction. Partial responses were achieved in 38% of evaluable patients, and in those patients who had greater than 50% CD22+ tumor cells, 50% of the patients achieved a partial response. Clinical responses were not related to tumor grade and were generally transient, lasting between 1 and 4 mo.

L28 ANSWER 29 OF 30 MEDLINE on STN DUPLICATE 11
 ACCESSION NUMBER: 90170197 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 2307538
 TITLE: Disseminated or localized growth of a **human**
 B-cell tumor (Daudi) in SCID mice.
 AUTHOR: Ghetie M A; Richardson J; Tucker T; Jones D; Uhr J W;
 Vitetta E S
 CORPORATE SOURCE: Department of Microbiology, University of Texas
 Southwestern Medical Center, Dallas 75235.
 SOURCE: International journal of cancer. Journal international du
 cancer, (1990 Mar 15) 45 (3) 481-5.
 Journal code: 0042124. ISSN: 0020-7136.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199004
 ENTRY DATE: Entered STN: 19900601
 Last Updated on STN: 19980206
 Entered Medline: 19900410

AB A **human** Burkitt lymphoma (Daudi) has been grown in the mutant mouse called C.B-17 SCID. Twenty-eight days after s.c. injection of Daudi cells, a palpable tumor grew only at the site of injection in all injected mice. In contrast, after intravenous (i.v.) or intraperitoneal (i.p.) injection, macroscopic, disseminated tumors developed. Following i.v. inoculation, tumors grew in the lungs, kidneys, ovaries and adipose tissue, and microscopic tumor infiltrates were observed in the spleen, bone marrow, spinal column and femur, whereas after i.p. injection, the tumors were localized in the abdomen, liver, spleen, ovaries and muscular tunics of the gut, but did not disseminate into the lung or bone marrow. The growth pattern and phenotype of the Daudi cells were similar whether the inoculated tumor cells were derived from the in vitro cell line or from in vivo passaged tumors. The survival time of the tumor-bearing animals was dependent on the dose of i.v.-administered Daudi cells; as few as 100 cells caused death. All mice injected i.v. showed paresis or paralysis of the hind legs just prior to death. This was associated with the presence of neoplastic nodules within the spinal canal. Two surface

CORPORATE SOURCE: Department of Microbiology, University of Texas
Southwestern Medical Center, Dallas 75235.

CONTRACT NUMBER: CA28149 (NCI)

CA42228 (NCI)

RR00890 (NCRR)

SOURCE: Cancer research, (1991 Nov 1) 51 (21) 5876-80.
Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199111

ENTRY DATE: Entered STN: 19920124

Last Updated on STN: 19980206

Entered Medline: 19911125

AB The antitumor effects of two anti-CD22 ricin A chain-containing immunotoxin (IT) constructs were compared in mice with severe combined immunodeficiency disease with human Daudi cell tumors (SCID-Daudi mice). SCID-Daudi mice develop disseminated lymphoma that clinically resembles African Burkitt's lymphoma, i.e., extranodal disease including infiltration of the vertebral column and spinal canal. In the absence of treatment, the mean survival time of SCID-Daudi mice was 45.9 +/- 4.3 days. The mice was given injections of a dose of IT equal to 40% of the 50% lethal dose. The ITs consisted of either IgG or Fab' fragments of mouse anti-CD22 antibody coupled to deglycosylated ricin A chain (dgA). Both ITs were potent and specific and inhibited protein synthesis in Daudi cells in vitro by 50% at concentrations of $1.2 \times 10(-12)$ (IgG-dgA) and $1.3 \times 10(-11)$ M (Fab'-dgA). When administered to mice beginning 1 day after inoculation with tumor cells, both ITs extended the mean survival time, to 87.2 +/- 18.9 days (IgG-dgA) or 57.9 +/- 3.8 days (Fab'-dgA). The latter represented the killing of 2 logs of Daudi cells, and the former 4 logs. IgG antibody alone killed 1 log of tumor cells. The IgG-dgA had an antitumor effect even when administered 20-23 days after tumor inoculation. Gross and histological examinations of IT-treated tumor-bearing mice showed a marked decrease in the number and size of neoplastic foci in both lymphoid organs and extranodal sites.

L28 ANSWER 28 OF 30 MEDLINE on STN

DUPLICATE 10

ACCESSION NUMBER: 91309090 MEDLINE

DOCUMENT NUMBER: PubMed ID: 1855219

TITLE: Phase I immunotoxin trial in patients with B-cell lymphoma.

AUTHOR: Vitetta E S; Stone M; Amlot P; Fay J; May R; Till M; Newman J; Clark P; Collins R; Cunningham D; +

CORPORATE SOURCE: Department of Microbiology, University of Texas
Southwestern Medical Center, Dallas 75235.

CONTRACT NUMBER:
CA-41081 (NCI)

SOURCE: Cancer research, (1991 Aug 1) 51 (15) 4052-8.
Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199108

ENTRY DATE: Entered STN: 19910913

Last Updated on STN: 19910913

Entered Medline: 19910828

L28 ANSWER 26 OF 30 MEDLINE on STN DUPLICATE 8
 ACCESSION NUMBER: 95299130 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 7780133
 TITLE: Continuous infusion of the anti-CD22 **immunotoxin**
 IgG-RFB4-SMPT-dgA in patients with B-cell lymphoma: a phase
 I study.
 AUTHOR: Sausville E A; Headlee D; Stetler-Stevenson M; Jaffe E S;
 Solomon D; Figg W D; Herdt J; Kopp W C; Rager H; Steinberg
 S M; +
 CORPORATE SOURCE: Laboratory of Biological Chemistry, National Cancer
 Institute, NIH, Bethesda, MD 20892, USA.
 CONTRACT NUMBER: CA-28149 (NCI)
 SOURCE: Blood, (1995 Jun 15) 85 (12) 3457-65.
 Journal code: 7603509. ISSN: 0006-4971.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: (CLINICAL TRIAL)
 (CLINICAL TRIAL, PHASE I)
 Journal; Article; (JOURNAL ARTICLE)
 (MULTICENTER STUDY)
 LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
 ENTRY MONTH: 199507
 ENTRY DATE: Entered STN: 19950726
 Last Updated on STN: 19950726
 Entered Medline: 19950720
 AB IgG-RFB4-SMPT-dgA consists of deglycosylated **ricin A chain (dgA)**
 coupled to the monoclonal **antihuman CD22 antibody**, RFB4. This study determined the maximally tolerated
 dose (MTD) of this **immunotoxin** (IT) administered as a continuous
 8-day infusion to 18 patients with B-cell lymphoma (30% CD22+ tumor cells)
 over 8 days. The MTD was 19.2 mg/m²/192 h (maximum toxicity grade 1),
 with vascular leak syndrome (VLS) as dose-limiting toxicity (DLT) at 28.8
 mg/m²/192 h (grades 3 through 5 in 7 of 11 patients). Predictors of
 severe VLS included serum IT concentrations greater than 1,000 ng/mL and
 the absence of circulating tumor cells. Decreased urine sodium excreted
 in 24 hours provided evidence for mild VLS without notable changes in
 serum albumin. Four partial responses, 3 minor responses, 6 stable
 disease, and 3 progression of disease were observed. The mean maximal
 serum concentration (Cmax) in initial courses at the MTD (19.2 mg/m²) was
 443 +/- 144 ng/mL (n = 3; range, 326 to 604). At 28.8 mg/m²/192 h, the
 Cmax was highly variable (n = 11; mean, 1,102 +/- 702; range, 9.6 to 2,032
 ng/mL). **Human antimouse or antiricin antibodies developed** in 6
 of 16 (37.5%) patients after one course of IT. However, 10 eligible
 patients received multiple courses of IT. Changes in serum cytokines and
 cytokine receptors did not correlate with toxicity but decreased soluble
 interleukin-2 receptor concentrations correlated with clinical response.
 Comparison to a prior study with the same IT administered by intermittent
 bolus infusions (Amlot et al, Blood 82:2624, 1993) suggests similar
 clinical response, toxicity, and immunogenicity.

L28 ANSWER 27 OF 30 MEDLINE on STN DUPLICATE 9
 ACCESSION NUMBER: 92034689 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 1933855
 TITLE: Antitumor activity of Fab' and IgG-anti-CD22
immunotoxins in disseminated **human B**
 lymphoma grown in mice with severe combined
 immunodeficiency disease: effect on tumor cells in
 extranodal sites.
 AUTHOR: Ghetie M A; Richardson J; Tucker T; Jones D; Uhr J W;
 Vitetta E S

is the antitumour antibiotic Calicheamicin theta. It offers an advantage over **immunotoxin** conjugates in that it involves coupling of a small molecule to the mAb thus avoiding potential immunogenicity. Furthermore its advantage over conventional **drug** conjugates such as **Doxorubicin**, is that it allows the delivery of therapeutic doses at practical concentrations (mg rather than gram quantities). We have demonstrated in cell culture that this agent coupled via enzymatically cleavable linkers (disulfide) to the mAb anti-CD19 is a potential candidate for clinical investigations.

L28 ANSWER 24 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 1999367297 EMBASE

TITLE: Low- versus high-dose radioimmunotherapy with
humanized anti-CD22 or **chimeric** anti-CD20
antibodies in a broad spectrum of B cell-associated
malignancies.

AUTHOR: Behr T.M.; Wormann B.; Gramatzki M.; Riggert J.; Gratz S.;
Behe M.; Griesinger F.; Sharkey R.M.; Kolb H.-J.; Hiddemann
W.; Goldenberg D.M.; Becker W.

CORPORATE SOURCE: T.M. Behr, Department of Nuclear Medicine,
Georg-August-University of Gottingen, Robert-Koch-Strasse
40, D-37075 Gottingen, Germany. tmbehr@med.uni-
goettingen.de

SOURCE: Clinical Cancer Research, (1999) 5/10 SUPPL. (3304s-3314s).
Refs: 24

ISSN: 1078-0432 CODEN: CCREF4

COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Both CD22 and CD20 have been used successfully as target molecules for radioimmunotherapy (RAIT) of low-grade B cell non-Hodgkin's lymphoma. Because both CD20 and CD22 are highly expressed relatively early in the course of B cell maturation, and because its expression is maintained up to relatively mature stages, we studied the potential of the **humanized anti-CD22 antibody**, hLL2, as well as of the **chimeric anti-CD20** (chCD20) antibody, rituximab (IDE-C2B8), for low- or high-dose (myeloablative) RAIT of a broad range of B cell-associated hematological malignancies. A total of 10 patients with chemorefractory malignant neoplasms of B cell origin were studied with diagnostic ($n = 5$) and/or potentially therapeutic doses ($n = 9$) of hLL2 ($n = 4$; 0.5 mg/kg, 8-315 mCi of ^{131}I) or chCD20 ($n = 5$; 2.5 mg/kg, 15-495 mCi of ^{131}I). The diagnostic doses were given to establish the patients' eligibility for RAIT and to estimate the individual radiation dosimetry. One patient suffered of Waldenstrom's macroglobulinemia, eight patients had low ($n = 4$), intermediate- ($n = 2$) or high- ($n = 2$) grade non-Hodgkin's lymphoma, and one patient had a chemorefractory acute lymphatic leukemia, after having failed five heterologous bone marrow or stem cell transplantations. Three of these 10 patients were scheduled for treatment with conventional (30-63 mCi, cumulated doses of up to 90 mCi of ^{131}I) and 7 with potentially myeloablative (225-495 mCi of ^{131}I) activities of ^{131}I -labeled hLL2 or chCD20 (0.5 and 2.5 mg/kg, respectively); homologous ($n = 6$) or heterologous ($n = 1$) stem cell support was provided in these cases. Good

ACCESSION NUMBER: 1988:215968 HCPLUS
DOCUMENT NUMBER: 108:215968
TITLE: Evaluation of ricin A chain-containing immunotoxins directed against CD19 and CD22 antigens on normal and malignant human B-cells as potential reagents for in vivo therapy
AUTHOR(S): Ghetie, Maria Ana; May, Richard D.; Till, Mark; Uhr, Jonathan W.; Ghetie, Victor; Knowles, Phillip P.; Relf, Michele; Brown, Alex; Wallace, Philip M.; et al.
CORPORATE SOURCE: Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235, USA
SOURCE: Cancer Research (1988), 48(9), 2610-17
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ricin A chain-containing immunotoxins (IT-As) specific for the human B-cell antigens CD22 and CD19 were constructed by using the monoclonal antibodies HD6 and HD37, resp. IT-As were prepared by coupling intact antibodies, F(ab')₂, or Fab' fragments to native or chemical deglycosylated ricin A chain. The IT-As were then evaluated for cytotoxicity to normal and neoplastic human B-cells in vitro with the major objective of appraising their suitability for in vivo therapy of human B-cell tumors. The IT-As prepared with both the HD6 and HD37 antibodies were specifically toxic to normal B-cells and to most of the neoplastic B-cell lines tested. However, the IT-As prepared from HD6 were generally more potent than those prepared from HD37. On Daudi cells, to which the 2 antibodies bound in similar nos. and with similar affinities, IT-As prepared with intact HD6 antibody or its Fab' fragment were 10-fold and 1.5-4-fold more potent, resp., than the corresponding HD37 IT-As. The IT-As constructed from intact HD6 antibody and native or deglycosylated A chain reduced protein synthesis in Daudi cells by 50% at a concentration of 1.2 + 10-11M, indicating that they were only 5-fold less toxic to the cells than ricin itself. Intact HD37 IT-As produced equivalent inhibition of protein synthesis at 1.5 + 10-10M. With both antibodies, IT-As constructed from the Fab' fragments were 10-20-fold less potent than their intact antibody counterparts. Different neoplastic B-cell lines varied in sensitivity to the IT-As. In most cases, their sensitivity correlated with the levels of CD19 and CD22 antigens expressed. Neither HD6 nor HD37 IT-As affected the ability of normal human bone marrow cells to form granulocyte-macrophage colony-forming units in soft agar, suggesting that both antigens are absent from these progenitor cells. The antibodies did not bind to a panel of normal tissues lacking B-lymphocytes. Apparently, HD6 and HD37 IT-As are candidates for in vivo therapy in humans with certain B-cell tumors. However, HD6 IT-As are more potent, reduce protein synthesis more completely, and hence appear to be the ITs of choice for treating tumors expressing the CD22 antigen.

CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The antitumor effects of two anti-CD22 **ricin A chain-containing immunotoxin** (IT) constructs were compared in mice with severe combined immunodeficiency disease with **human** Daudi cell tumors (SCID-Daudi mice). SCID-Daudi mice develop disseminated lymphoma that clin. resembles African Burkitt's lymphoma, i.e., extranodal disease including infiltration of the vertebral column and spinal canal. In the absence of treatment, the mean survival time of SCID-Daudi mice was 45.9 days. The mice were given injections of a dose of IT equal to 40% of the 50% LD. The ITs consisted of either IgG or Fab' fragments of mouse **anti-CD22 antibody** coupled to deglycosylated **ricin A chain** (dgA). Both ITs were potent and specific and inhibited protein synthesis in Daudi cells in vitro by 50% at concns. of 1.2 + 10-12 (IgG-dgA) and 1.3 + 10-11M (Fab'-dgA). When administered to mice beginning 1 day after inoculation with tumor cells, both ITs extended the mean survival time, to 87.2 days (IgG-dgA) or 57.9 days (Fab'-dgA). The latter represented the killing of 2 logs of Daudi cells, and the former 4 logs. IgG antibody alone killed 1 log of tumor cells. The IgG-dgA had an antitumor effect even when administered 20-23 days after tumor inoculation. Gross and histol. examns. of IT-treated tumor-bearing mice showed a marked decrease in the number and size of neoplastic foci in both lymphoid organs and extranodal sites.

L26 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1989:37496 HCAPLUS
 DOCUMENT NUMBER: 110:37496
 TITLE: The epitope specificity and tissue reactivity of four murine monoclonal **anti-CD22 antibodies**
 AUTHOR(S): Li, Jia Ling; Shen, Guo Liang; Ghetie, Maria Ana; May, Richard D.; Till, Mark; Ghetie, Victor; Uhr, Jonathan W.; Janossy, George; Thorpe, Philip E.; et al.
 CORPORATE SOURCE: Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235, USA
 SOURCE: Cellular Immunology (1989), 118(1), 85-99
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The CD22 antigen is expressed on the surface of normal **human B** cells and some neoplastic B cell lines and tumors. Previous cross-blocking studies using a panel of monoclonal **anti-CD22 antibodies** have defined 4 epitope groups, termed A-D. In the present studies, the epitopes recognized by 4 monoclonal **anti-CD22 antibodies** were further dissected using immunopptn. and cross-blocking techniques, immunofluorescence analyses with a variety of cell lines, and immunoperoxidase analyses of 36 normal **human** tissues. Two of the antibodies, HD6 and RFB4, have been described previously, and 2, UV22-1 and UV22-2, are described in this report. The 4 monoclonal antibodies showed unexpected complexities in their reactivity with CD22+ and CD22- cells and their reactivity with solubilized CD22 mols. The 4 antibodies, which recognize epitopes defined previously as CD22-A and CD22-B, further subdivide these epitope clusters into 4 determinants, A1, A2, B1, and B2. Furthermore, only 2 of the antibodies, RFB4 and UV22-2, are B cell-specific. Thus, RFB4 and UV22-2 would be the antibodies of choice for constructing **immunotoxins** to treat B cell tumors.

L26 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

progression fo disease were observed. The mean amximal serum concentration (Cmax) in

initial courses at the MTD (19.2 mg/m²) was 443 ± 144 ng/mL (n = 3; range, 326 to 604). At 28.8 m/m²/192 h, the Cmax was highly variable (n = 11; mean, 1,102 ± 702; range, 9.6 to 2,032 ng/mL). **Human** antimouse or antiricin antibodies developed in 6 of 16 (37.5%) patients after one course of IT. However, 10 eligible patients received multiple courses of IT. Changes in serum cytokines and cytokine receptors did not correlate with toxicity but decreased soluble interleukin-2 receptor concns. correlated with clin. response. Comparison to a prior study with the same IT administered by intermittent bolus infusions (Amlot et al., Blood 82:2624, 1993) suggests similar clin. response, toxicity, and immunogenicity.

L26 ANSWER 18 OF 21 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:214842 HCPLUS

DOCUMENT NUMBER: 120:214842

TITLE: Anti-CD19 inhibits the growth of **human**

B-cell tumor lines in vitro and of Daudi cells in SCID mice by inducing cell cycle arrest

AUTHOR(S): Ghetie, Maria Ana; Picker, Louis J.; Richardson, James A.; Tucker, Karsten; Uhr, Jonathan W.; Vitetta, Ellen S.

CORPORATE SOURCE: Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235-8576, USA

SOURCE: Blood (1994), 83(5), 1329-36

CODEN: BLOOAW; ISSN: 0006-4971

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors extend their previous findings that IgG or F(ab')2 fragments of HD37 anti-CD19 antibody (Ab) in combination with the **immunotoxin** (IT), RFB4-anti-CD11-deglycosylated ricin A chain (dgA) (but neither reagent alone), prolonged the survival of SCID mice with disseminated **human** Daudi lymphoma (SCID/Daudi mice) to 1 yr at which time they still remained tumor-free. The authors explored the mechanisms by which the HD37 Ab exerts antitumor activity in vivo by studying its activity in vitro. It has antiproliferative activity (IC₅₀ = 5.2 - 9.8 + 10⁻⁷ mol/L) on three CD19+ Burkitt's lymphoma cell lines (Daudi, Raji, and Namalwa) but not on a weakly CD19-pos. (CD19lo) pre-B cell tumor (Nalm-6). The inhibitory effect was manifested by cell cycle arrest, but not apoptosis. Results using three addnl. anti-CD19 Abs, suggest that the affinity of the antibody and possibly the epitope which it recognizes may effect its capacity to transmit a signal that induces cell cycle arrest. Hence, therapeutically useful Abs may exert anti-tumor activity by a variety of mechanisms, each of which should be evaluated before undertaking clin. trials in **humans**.

L26 ANSWER 19 OF 21 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1992:51018 HCPLUS

DOCUMENT NUMBER: 116:51018

TITLE: Antitumor activity of Fab' and IgG-anti-CD22

immunotoxins in disseminated **human** B lymphoma grown in mice with severe combined immunodeficiency disease: effect on tumor cells in extranodal sites

AUTHOR(S): Ghetie, Maria Ana; Richardson, James; Tucker, Thomas; Jones, Diane; Uhr, Jonathan W.; Vitetta, Ellen S.

CORPORATE SOURCE: Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235, USA

SOURCE: Cancer Research (1991), 51(21), 5876-80

EP 969866	A1	20000112	EP 1998-912936	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001518930	T2	20011016	JP 1998-545761	19980317
EP 1431311	A1	20040623	EP 2004-75775	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1459768	A2	20040922	EP 2004-75774	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
ZA 9802438	A	19981104	ZA 1998-2438	19980323
US 1997-41506P P 19970324				
EP 1998-912936 A3 19980317				
WO 1998-US5075 W 19980317				
PRIORITY APPLN. INFO.:				

AB B-Cell malignancies, such as the B-cell subtype of non-Hodgkin's lymphoma and chronic lymphocytic leukemia, are significant contributors to cancer mortality. The response of B-cell malignancies to various forms of treatment is mixed. Traditional methods of treating B-cell malignancies, including chemotherapy and radiotherapy, have limited utility due to toxic side effects. Immunotherapy with anti-CD20 antibodies have also provided limited success. The use of antibodies that bind with the CD22 antigen, however, provides an effective means to treat B-cell malignancies such as indolent and aggressive forms of B-cell lymphomas, and acute and chronic forms of lymphatic leukemias. Moreover, immunotherapy with **anti-CD22 antibodies** requires comparatively low doses of antibody protein, and can be used effectively in multimodal therapies. Immunoconjugates comprising **anti-CD22 antibody** and **radioisotope** or cytokine, and combination treatment with chemotherapeutic agent are also disclosed.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1995:637554 HCAPLUS
 TITLE: Continuous infusion of the anti-CD22 immunotoxin IgG-RFB4-SMPT-dgA in patients with B-cell lymphoma: a phase I study
 AUTHOR(S): Sausville, Edwards A.; Headlee, Donna; Stetler-Stevenson, Maryalice; Jaffe, Elaine S.; Solomon, Diane; Figg, William D.; Herdt, Jean; Kopp, William C.; Rager, Helen; et al.

CORPORATE SOURCE: Labs. Biological Chem. Pathology, Natl. Cancer Inst., Bethesda, MD, USA

SOURCE: Blood (1995), 85(12), 3457-65
 CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: Saunders

DOCUMENT TYPE: Journal

LANGUAGE: English

AB IgG-RFB4-SMPT-dgA consists of deglycosylated ricin A chain (dgA) coupled to the monoclonal **antihuman CD22 antibody**, RFB4. This study determined the maximally tolerated dose (MTD) of this **immunotoxin** (IT) administered as a continuous 8-day infusion to 18 patients with B-cell lymphoma (30% CD22+ tumor cells) over 8 days. The MTD was 19.2 mg/m²/192 h (maximum toxicity grade 1), with vascular leak syndrome (VLS) as dose-limiting toxicity (DLT) at 28.8 mg/m²/192 h (grades 3 through 5 in 7 of 11 patients). Predictors of severe VLS included serum IT concns. greater than 1,000 ng/mL and the absence of circulating tumor cells. Decreased urine sodium excreted in 24 h provided evidence for mild VLS without notable changes in serum albumin. Four partial responses, 3 minor responses, 6 stable disease, and 3

Inventor Search

Harris 09/965,796

08/12/2004

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L4 ANSWER 1 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:934160 HCPLUS
DOCUMENT NUMBER: 141:388650
TITLE: Anti-CD74 immunoconjugates and their therapeutic and diagnostic uses
INVENTOR(S): Griffiths, Gary L.; Hansen, Hans J.; **Goldenberg, David M.**; Lundberg, Bo B.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 44 pp., Cont.-in-part of U.S. Ser. No. 377,122.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004219203	A1	20041104	US 2003-706852	20031112
US 6306393	B1	20011023	US 1999-307816	19990510
US 2002071807	A1	20020613	US 2001-965796	20011001
US 2003124058	A1	20030703	US 2002-314330	20021209
US 2003133930	A1	20030717	US 2003-350096	20030124
US 2004115193	A1	20040617	US 2003-377122	20030303
PRIORITY APPLN. INFO.:			US 1999-307816	A1 19990510
			US 2000-590284	A1 20000609
			US 2001-965796	A1 20011001
			US 2002-360259P	P 20020301
			US 2002-314330	A2 20021209
			US 2003-350096	A2 20030124
			US 2003-377122	A2 20030303
			US 2003-478830P	P 20030617
			US 1997-41506P	P 19970324
			US 1998-38995	A2 19980312
			US 1999-138284P	P 19990609

AB Disclosed are compns. that include anti-CD74 immunoconjugates and a therapeutic and/or diagnostic agent. Also disclosed are methods for preparing the immunoconjugates and using the immunoconjugates in diagnostic and therapeutic procedures. The compns. may be part of a kit for administering the anti-CD74 immunoconjugates compns. in therapeutic and/or diagnostic methods. Anti-CD74 binding mols. are conjugated to the one or more lipids by one or more of a sulfide linkage, a hydrazone linkage, a hydrazine linkage, an ester linkage, an amido linkage, an amino linkage, an imino linkage, a thiosemicarbazone linkage, a semicarbazone linkage, an oxime linkage, a carbon-carbon linkage. Anti-CD74 immunoconjugates comprise a drug, a prodrug, a toxin, an enzyme, a radioisotope, an immunomodulator, a cytokine, a hormone, an antibody., an oligonucleotide, or a photodynamic agent.

L4 ANSWER 2 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:565117 HCPLUS
DOCUMENT NUMBER: 141:122334
TITLE: **Immunotherapy of B cell**
malignancies and autoimmune disease using unconjugated and conjugated antibodies, fragments or fusion proteins
INVENTOR(S): **Goldenberg, David M.**; Hansen, Hans
PATENT ASSIGNEE(S): Immunomedics, Inc., USA; McCall, John Douglas

SOURCE: PCT Int. Appl., 49 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004058298	A1	20040715	WO 2003-GB5700	20031231
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004219156	A1	20041104	US 2003-747199	20031230

PRIORITY APPLN. INFO.: US 2002-437145P P 20021231

AB The invention is directed to a method for treating a treating and diagnosing a B cell-related disease, T cell-related disease or an autoimmune disease in a mammal by concurrently or sequentially administering to the mammal a therapeutic composition that comprises a pharmaceutically acceptable vehicle and at least one conjugated antibody, wherein predosing with a non-radiolabeled antibody is not performed. The target antigen of the unconjugated and conjugated antibody is CD3, CD4, CD5, CD8, CD11c, CD14, CD15, CD19, CD20, CD21, CD22, CD23, CD25, CD33, CD37, CD38, CD40, CD40L, CD46, CD52, CD54, CD74, CD80, CD126, MUC1, tenascin, Ia, HMI.24, HLA-DR and tumor antigen. The antibody is human, murine, chimeric, primatized or humanized antibody. The antibody is conjugated with therapeutic agent selected from drug, toxin, immunomodulator, chelator, boron compound, photoactive agent or radionuclide.

L4 ANSWER 3 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:847740 HCPLUS
 DOCUMENT NUMBER: 140:215693
 TITLE: Epratuzumab: targeting B-cell malignancies through CD22
 AUTHOR(S): Coleman, Morton; Goldenberg, David M.; Siegel, Abby B.; Ketas, Jamie C.; Ashe, Michelle; Fiore, Jennifer M.; Leonard, John P.
 CORPORATE SOURCE: Center for Lymphoma and Myeloma, Division of Hematology/Oncology, Weill Medical College of Cornell University and New York Presbyterian Hospital, New York, NY, 10021, USA
 SOURCE: Clinical Cancer Research (2003), 9(10, Pt. 2), 3991s-3994s
 PUBLISHER: American Association for Cancer Research
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review. The development of effective B cell -directed monoclonal antibody therapies has dramatically altered the management of patients with B-cell non-Hodgkin's lymphoma. Anti-CD20 murine and chimeric antibodies have been

characterized by manageable toxicity profiles and appear to have mechanisms which may be distinct from and complementary to those of chemotherapy. There is considerable rationale for treatment strategies which target other B-cell antigens, including CD22. This mol. is commonly expressed in non-Hodgkin's lymphoma and may mediate important functions in B-cell biol. Laboratory and initial clin. studies suggest that epratuzumab, a humanized anti-

CD22 monoclonal antibody, may have antilymphoma activity in both unlabeled and radiolabeled forms. Efforts are underway to establish the utility of epratuzumab as a treatment for B-cell malignancies, through single agent and combination regimens, to define the optimal settings for its clin. application.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:739535 HCPLUS
 DOCUMENT NUMBER: 139:290733
 TITLE: CD22-directed monoclonal antibody therapy for lymphoma
 AUTHOR(S): Siegel, Abby B.; Goldenberg, David M.; Cesano, Alessandra; Coleman, Morton; Leonard, John P.
 CORPORATE SOURCE: Center for Lymphoma and Myeloma, Division of Hematology/Oncology, Weill Medical College of Cornell University and New York Presbyterian Hospital, New York, NY, USA
 SOURCE: Seminars in Oncology (2003), 30(4), 457-464
 CODEN: SOLGAV; ISSN: 0093-7754
 PUBLISHER: W. B. Saunders Co.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. Immunotherapy directed against the CD20 antigen has had a profound impact on the management of patients with B-cell non-Hodgkin's lymphoma (NHL). Antibody-based treatments offer a favorable side effect profile, as well as alternate mechanisms of action that may complement those of cytotoxic modalities. Targeting other antigens, such as CD22, may also result in antilymphoma effects. This B-cell-specific mol. is widely expressed in NHL and mediates important functions in B-cell biol. Preclin. and early clin. data suggest that epratuzumab, a humanized anti-CD22 monoclonal antibody, demonstrates antilymphoma effects in both unlabeled and radiolabeled forms, as well as a favorable safety profile. Ongoing and future studies will further determine the role of epratuzumab among the array of antilymphoma therapies, both as a single agent and in combination with other agents.

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:719519 HCPLUS
 DOCUMENT NUMBER: 139:259963
 TITLE: Anti-CD74 antibodies and conjugates for diagnosis and treatment of immune and autoimmune diseases, infections and cancers
 INVENTOR(S): Hansen, Hans; Leung, Shui-on; Qu, Zhengxing; Goldenberg, David M.
 PATENT ASSIGNEE(S): Immunomedics, Inc., USA; McCall, John Douglas
 SOURCE: PCT Int. Appl., 91 pp.
 CODEN: PIXXD2

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 7
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003074567	A2	20030912	WO 2003-GB890	20030303
WO 2003074567	A3	20031231		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 2002-360259P P 20020301
 AB The present invention provides humanized, chimeric and human anti-CD74 antibodies, CD74 antibody fusion proteins, immunoconjugates, vaccines and bispecific that bind to CD74, the major histocompatibility complex (MHC) class-II invariant chain, Ii, which is useful for the treatment and diagnosis of B-cell disorders, such as B-cell malignancies, other malignancies in which the cells are reactive with CD74, and autoimmune diseases, and methods of treatment and diagnosis.

L4 ANSWER 6 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:656808 HCPLUS
 DOCUMENT NUMBER: 139:196278
 TITLE: Anti-CD20 antibodies and fusion proteins for diagnosis and treatment of B cell disease, B cell malignancy and autoimmune diseases
 INVENTOR(S): Hansen, Hans; Qu, Zhengxing; Goldenberg, David M.
 PATENT ASSIGNEE(S): Immunomedics, Inc., USA; McCall, John Douglas
 SOURCE: PCT Int. Appl., 106 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068821	A2	20030821	WO 2003-GB665	20030214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2003219433	A1	20031127	US 2003-366709	20030214

PRIORITY APPLN. INFO.: US 2002-356132P P 20020214
US 2002-416232P P 20021007

AB The present invention provides humanized, chimeric and human anti-CD20 antibodies and CD20 antibody fusion proteins that bind to a human B cell marker, referred to as CD20, which is useful for the treatment and diagnosis of B-cell disorders, such as B-cell malignancies and autoimmune diseases, and methods of treatment and diagnosis.

L4 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:276421 HCAPLUS
 DOCUMENT NUMBER: 136:278150
 TITLE: **Immunotherapy** of malignant and autoimmune disorders in domestic animals using naked antibodies, immunoconjugates and fusion proteins
 INVENTOR(S): Goldenberg, David M.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 17 pp., Cont.-in-part of U.S. 6,134,982.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 7
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002041847	A1	20020411	US 2001-921290	20010803
US 6306393	B1	20011023	US 1999-307816	19990510
PRIORITY APPLN. INFO.:			US 1998-38995	A2 19980312
			US 1999-307816	A2 19990510
			US 1997-41506P	P 19970324

AB B-cell, T-cell, myeloid-cell, mast-cell, and plasma-cell disorders are significant contributors to illness and mortality in domestic animals, especially in companion animals such as dogs and cats. These disorders include both autoimmune disorders and malignancies, such as the B-cell subtype of non-Hodgkin's lymphoma, acute and chronic lymphocytic or myeloid leukemias, multiple myeloma, and mastocytomas. Antibody components that bind with B-cell or T-cell antigens or epitopes, as well as antigens or epitopes of myeloid, plasma and mast cells provide an effective means to treat these disorders in domestic animals. The **immunotherapy** uses naked antibodies, immunoconjugates and fusion proteins, alone or in combination with standard therapeutic regimens.

L4 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:771011 HCAPLUS
 DOCUMENT NUMBER: 135:317474
 TITLE: **Immunotherapy of B-cell**
 malignancies using anti-CD22 antibodies
 INVENTOR(S): Goldenberg, David M.
 PATENT ASSIGNEE(S): Immunomedics, Inc., USA
 SOURCE: U.S., 14 pp., Cont.-in-part of U.S. 6,183,744.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 7
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 6306393	B1	20011023	US 1999-307816	19990510
EP 1431311	A1	20040623	EP 2004-75775	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1459768	A2	20040922	EP 2004-75774	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CA 2373618	AA	20001116	CA 2000-2373618	20000510
WO 2000067795	A1	20001116	WO 2000-US12583	20000510
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2000048296	A5	20001121	AU 2000-48296	20000510
AU 774044	B2	20040617		
EP 1178826	A1	20020213	EP 2000-930484	20000510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002544173	T2	20021224	JP 2000-616820	20000510
US 2002041847	A1	20020411	US 2001-921290	20010803
US 2002071807	A1	20020613	US 2001-965796	20011001
US 2003124058	A1	20030703	US 2002-314330	20021209
US 2004219203	A1	20041104	US 2003-706852	20031112
PRIORITY APPLN. INFO.:				
US 1997-41506P P 19970324				
US 1998-38995 A2 19980312				
EP 1998-912936 A3 19980317				
US 1999-307816 A 19990510				
WO 2000-US12583 W 20000510				
US 2000-590284 A1 20000609				
US 2001-965796 A1 20011001				
US 2002-360259P P 20020301				
US 2002-314330 A2 20021209				
US 2003-350096 A2 20030124				
US 2003-377122 A2 20030303				
US 2003-478830P P 20030617				

AB **B-cell** malignancies, such as the **B-cell** subtype of non-Hodgkin's lymphoma and chronic lymphocytic leukemia, are significant contributors to cancer mortality. The response of **B-cell** malignancies to various forms of treatment is mixed. Traditional methods of treating **B-cell** malignancies, including chemotherapy and radiotherapy, have limited utility due to toxic side effects. **Immunotherapy** with anti-CD20 antibodies have also provided limited success. The use of antibodies that bind with the CD22 or CD19 antigen, however, provides an effective means to treat **B-cell** malignancies such as indolent and aggressive forms of **B-cell** lymphomas, and acute and chronic forms of lymphatic leukemias. Moreover, **immunotherapy** with anti-CD22 and/or anti-CD19 antibodies requires comparatively low doses of antibody protein, and can be used effectively in multimodal therapies.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:880995 HCAPLUS
 DOCUMENT NUMBER: 134:41104
 TITLE: **Immunotherapy** of autoimmune disorders using antibodies which target B-cells
 INVENTOR(S): **Goldenberg, David M.**; Hansen, Hans J.
 PATENT ASSIGNEE(S): Immunomedics, Inc., USA
 SOURCE: PCT Int. Appl., 39 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 7
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000074718	A1	20001214	WO 2000-US15780	20000609
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2375912	AA	20001214	CA 2000-2375912	20000609
EP 1194167	A1	20020410	EP 2000-941278	20000609
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.:			US 1999-138284P	P 19990609
			WO 2000-US15780	W 20000609

AB Antibodies that bind with a **B-cell** antigen provide an effective means to treat autoimmune disorders. Antibodies and fragments, which may be conjugated or naked, are used alone or in multimodal therapies. The antibodies may be bispecific antibodies which may be produced recombinantly as fusion proteins, or as hybrid, polyspecific antibodies.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:814346 HCAPLUS
 DOCUMENT NUMBER: 133:361914
 TITLE: **Immunotherapy** of **B-cell** malignancies using anti-CD22 antibodies
 INVENTOR(S): **Goldenberg, David M.**
 PATENT ASSIGNEE(S): Immunomedics, Inc., USA
 SOURCE: PCT Int. Appl., 52 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 7
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067795	A1	20001116	WO 2000-US12583	20000510
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,				

LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
 SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
 ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
 DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
 CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 US 6306393 B1 20011023 US 1999-307816 19990510
 CA 2373618 AA 20001116 CA 2000-2373618 20000510
 AU 2000048296 A5 20001121 AU 2000-48296 20000510
 AU 774044 B2 20040617
 EP 1178826 A1 20020213 EP 2000-930484 20000510
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO
 JP 2002544173 T2 20021224 JP 2000-616820 20000510
 PRIORITY APPLN. INFO.: US 1999-307816 A2 19990510
 US 1997-41506P P 19970324
 US 1998-38995 A2 19980312
 WO 2000-US12583 W 20000510

AB **B-cell** malignancies, such as the **B-cell** subtype of non-Hodgkin's lymphoma and chronic lymphocytic leukemia, are significant contributors to cancer mortality. The response of **B-cell** malignancies to various forms of treatment is mixed. Traditional methods of treating **B-cell** malignancies, including chemotherapy and radiotherapy, have limited utility due to toxic side effects. **Immunotherapy** with anti-CD20 antibodies have also provided limited success. The use of antibodies that bind with the CD22 or CD19 antigen, however, provides an effective means to treat **B-cell** malignancies such as indolent and aggressive forms of **B-cell** lymphomas, and acute and chronic forms of lymphatic leukemias. Moreover, **immunotherapy** with anti-CD22 and/or anti-CD19 antibodies requires comparatively low doses of antibody protein, and can be used effectively in multimodal therapies.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1999:740269 HCPLUS
 DOCUMENT NUMBER: 131:319707
 TITLE: Low- versus high-dose **radioimmunotherapy**
 with humanized anti-CD22 or chimeric
 anti-CD20 antibodies in a broad spectrum of **B**
cell-associated malignancies
 AUTHOR(S): Behr, Thomas M.; Wormann, Bernhard; Gramatzki, Martin;
 Riggert, Joachim; Gratz, Stefan; Behe, Martin;
 Griesinger, Frank; Sharkey, Robert M.; Kolb, Hans-J.;
 Hiddemann, Wolfgang; Goldenberg, David M.;
 Becker, Wolfgang
 CORPORATE SOURCE: Departments of Nuclear Medicine, Georg-August-
 University of Gottingen, Gottingen, D-37075, Germany
 SOURCE: Clinical Cancer Research (1999), 5(10, Suppl.),
 3304s-3314s
 CODEN: CCREF4; ISSN: 1078-0432
 PUBLISHER: American Association for Cancer Research
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Both CD22 and CD20 have been used successfully as target mols.
 for **radioimmunotherapy** (RAIT) of low-grade **B**
 cell non-Hodgkin's lymphoma. Because both CD20 and CD22
 are highly expressed relatively early in the course of **B**

cell maturation, and because its expression is maintained up to relatively mature stages, we studied the potential of the humanized anti-CD22 antibody, hLL2, as well as of the chimeric anti-CD20 (chCD20) antibody, rituximab (IDE-C2B8), for low- or high-dose (myeloablative) RAIT of a broad range of B cell-associated hematol-malignancies. A total of 10 patients with chemorefractory malignant neoplasms of B cell origin were studied with diagnostic (n = 5) and/or potentially therapeutic doses (n = 9) of hLL2 (n = 4; 0.5 mg/kg, 8-315 mCi of 131I) or chCD20 (n = 5; 2.5 mg/kg, 15-495 mCi of 131I). The diagnostic doses were given to establish the patients' eligibility for RAIT and to estimate the individual radiation dosimetry. One patient suffered of Waldenstrom's macroglobulinemia, eight patients had low- (n = 4), intermediate- (n = 2) or high- (n = 2) grade non-Hodgkin's lymphoma, and one patient had a chemorefractory acute lymphatic leukemia, after having failed five heterologous bone marrow or stem cell transplantations. Three of these 10 patients were scheduled for treatment with conventional (30-63 mCi, cumulated doses of up to 90 mCi of 131I) and 7 with potentially myeloablative (225-495 mCi of 131I) activities of 131I-labeled hLL2 or chCD20 (0.5 and 2.5 mg/kg, resp.); homologous (n = 6) or heterologous (n = 1) stem cell support was provided in these cases. Good tumor targeting was observed in all diagnostic as well as posttherapeutic scans of all patients. In myeloablative therapies, the therapeutic activities were calculated based on the diagnostic radiation dosimetry, aiming at lung and kidney doses < 20Gy. Stem cells were reinfused when the whole-body activity retention fell below 20 mCi. In eight assessable patients, five had complete remissions, two experienced partial remissions (corresponding to an overall response rate of 87%), and one (low-dose) patient had progressive disease despite therapy. In the five assessable, actually stem-cell grafted patients, the complete response rate was 100%. Both CD20 and CD22 seem to be suitable target mol. for high-dose RAIT in a broad spectrum of hematol-malignancies of B cell origin with a broad range of maturation stages (from acute lymphatic leukemia to Waldenstrom's macroglobulinemia). The better therapeutic outcome of patients undergoing high-dose, myeloablative RAIT favors this treatment concept over conventional, low-dose regimens.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1998:661515 HCPLUS
 DOCUMENT NUMBER: 129:274703
 TITLE: Immunotherapy of B-cell malignancies using anti-CD22 antibodies
 INVENTOR(S): Goldenberg, David M.
 PATENT ASSIGNEE(S): IMMUNOMEDICS, INC., USA
 SOURCE: PCT Int. Appl., 41 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 7
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9842378	A1	19981001	WO 1998-US5075	19980317
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA,				

UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
 FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,
 GA, GN, ML, MR, NE, SN, TD, TG

US 6183744	B1	20010206	US 1998-38955	19980312
CA 2284829	AA	19981001	CA 1998-2284829	19980317
AU 9867610	A1	19981020	AU 1998-67610	19980317
AU 728325	B2	20010104		
EP 969866	A1	20000112	EP 1998-912936	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001518930	T2	20011016	JP 1998-545761	19980317
EP 1431311	A1	20040623	EP 2004-75775	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1459768	A2	20040922	EP 2004-75774	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
ZA 9802438	A	19981104	ZA 1998-2438	19980323
PRIORITY APPLN. INFO.:				
			US 1997-41506P	P 19970324
			EP 1998-912936	A3 19980317
			WO 1998-US5075	W 19980317

AB **B-Cell malignancies, such as the B-cell subtype of non-Hodgkin's lymphoma and chronic lymphocytic leukemia, are significant contributors to cancer mortality. The response of B-cell malignancies to various forms of treatment is mixed. Traditional methods of treating B-cell malignancies, including chemotherapy and radiotherapy, have limited utility due to toxic side effects. Immunotherapy with anti-CD20 antibodies have also provided limited success. The use of antibodies that bind with the CD22 antigen, however, provides an effective means to treat B-cell malignancies such as indolent and aggressive forms of B-cell lymphomas, and acute and chronic forms of lymphatic leukemias. Moreover, immunotherapy with anti-CD22 antibodies requires comparatively low doses of antibody protein, and can be used effectively in multimodal therapies. Immunoconjugates comprising anti-CD22 antibody and radioisotope or cytokine, and combination treatment with chemotherapeutic agent are also disclosed.**

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1998:440581 HCPLUS
 DOCUMENT NUMBER: 129:186201
 TITLE: CD22 is a suitable target molecule for detection and high-dose, myeloablative radioimmunotherapy with the monoclonal antibody LL2 in acute lymphatic leukemia and Waldenstrom's macroglobulinemia
 AUTHOR(S): Behr, Thomas M.; Holler, Ernst; Gratz, Stefan; Wormann, Bernhard; Sharkey, Robert M.; Dunn, Robert M.; Hidemann, Wolfgang; Kolb, Hans-Joachim; Goldenberg, David M.; Becker, Wolfgang
 CORPORATE SOURCE: Dep. of Nuclear Med., Georg-August Univ., Goettingen, Germany
 SOURCE: Tumor Targeting (1998), 3(1), 32-40
 CODEN: TUTAF9; ISSN: 1351-8488
 PUBLISHER: Stockton Press
 DOCUMENT TYPE: Journal

LANGUAGE: English

AB CD22 is a 135 kDa glycoprotein of the Ig superfamily which is expressed on most B lymphocytes. It has been used successfully as a target mol. for radioimmunodetection and therapy of B-cell non-Hodgkin's lymphoma with the monoclonal antibody CD22 (Mab), LL2. Since CD22 is highly expressed on blasts in acute lymphatic leukemia of B-cell origin as well as on the malignant lymphocytes of macroglobulinemia, we studied the potential of LL2 for the detection and therapy of these two haematol. malignancies in two pilot cases. A 43-yr-old male suffered from macroglobulinemia, first diagnosed 4 yr earlier. The IgM produced by the malignant clone cross-reacted with a ganglioside of peripheral neurons, causing severe and progressive sensorimotor neuropathy. Several bone marrow biopsies as well as a splenectomy were not able to demonstrate the presence of a malignant clone which would be responsible for the IgM production. A localized tumor was suspected, but was not detected by any radiol. procedure. Thus, the patient underwent radioimmunodetection (RAID) with ^{99m}Tc -LL2 Fab1 (LymphoScan). The second patient was a 28-yr-old male who had common acute lymphatic leukemia (c-ALL) for 8 yr. He had failed 6 high-dose chemotherapy regimens with allogenic bone marrow or stem cell transplantations from his HLA-compatible brother. The patient had also failed two immunotherapeutic approaches with bispecific murine antibodies, which had caused high titers of HAMA. The patient was treated with high-dose radioimmunotherapy with $^{131\text{I}}$ -labeled humanized LL2 IgG in myeloablative intention with stem cell support. Although all diagnostic procedures had failed in the macroglobulinemia patient, ^{99m}Tc -LL2 Fab1 showed excellent targeting of widespread para-iliac, mediastinal, axillary and cervical lymph node involvement (all smaller than 1 cm in size) as well as a patchy uptake all over the patient's bone marrow as a sign of generalized tumor infiltration, precluding any localized treatment approach, such as external beam irradiation. The c-ALL patient underwent a diagnostic study with humanized LL2 (50 mg of protein, 8 mCi $^{131\text{I}}$) in order to assess tumor targeting and dosimetry, and was treated based on the result, with 258 mCi hLL2 at the same protein dose. Strong uptake occurred in the patient's bone marrow as well as in several extramedullary tumor sites (lymph nodes, spleen, muscular infiltration of the thigh). At a marrow dose of 30 Gy (whole-body 3.5 Gy, lung 12 Gy), the patient went into complete remission and bone marrow aplasia within two days. Reengraftment of the red marrow took place rapidly. The patient experienced a complete remission lasting for 7 wk. Relapsed ALL and Waldenstrom's macroglobulinemia seem to be suitable targets for a radioimmunotherapeutic approach with the anti-CD22 monoclonal antibody, LL2. Future studies will show whether high-dose RAIT with heterologous stem cell support may be able to induce longer-lasting remissions or even be curative in these haematol. malignancies.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:439188 HCPLUS

DOCUMENT NUMBER: 127:132770

TITLE: Advantage of residualizing radiolabels for an internalizing antibody against the B-cell lymphoma antigen, CD22

AUTHOR(S): Sharkey, Robert M.; Behr, Thomas M.; Mattes, M. Jules; Stein, Rhona; Griffiths, Gary L.; Shih, Lisa B.; Hansen, Hans J.; Blumenthal, Rosalyn D.; Dunn, Robert M.; Juweid, Malik E.; Goldenberg, David M.

CORPORATE SOURCE: The Garden State Cancer Center, Belleville, NJ, 07109,

USA

SOURCE: Cancer Immunology Immunotherapy (1997), 44(3), 179-188
 CODEN: CIIMDN; ISSN: 0340-7004

PUBLISHER: Springer
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB LL2 is an anti-CD22 pan-B-cell monoclonal antibody which, when radiolabeled, has a high sensitivity for detecting B-cell, non-Hodgkin's lymphoma (NHL), as well as an antitumor efficacy in therapeutic applications. The aim of this study was to determine whether intracellularly retained radiolabels have an advantage in the diagnosis and therapy of lymphoma with LL2. In vitro studies showed that iodinated LL2 is intracellularly catabolized, with a rapid release of the radioiodine from the cell. In contrast, residualizing radiolabels, such as radioactive metals, are retained intracellularly for substantially longer. In vivo studies were performed using LL2-labeled with radioiodine by a non-residualizing (chloramine-T) or a residualizing method (dilactitol-tyramine, DLT), or with a radioactive metal (¹¹¹In). The biodistribution of a mixture of ¹²⁵I (non-residualizing chloramine-T compared to residualizing DLT), ¹¹¹In-labeled LL2 murine IgG2a or its fragments [F(ab')₂, Fab'], as well as its humanized, CDR-grafted form, was studied in nude mice bearing the RL human B-cell NHL cell line. Radiation doses were calculated from the biodistribution data according to the Medical International Radiation Dose scheme to assess the potential advantage for therapeutic applications. At all assay times, tumor uptake was higher with the residualizing labels (i.e., ¹¹¹In and DLT-¹²⁵I) than with the non-residualizing iodine label. For example, tumor/blood ratios of ¹¹¹In-labeled IgG were 3.2-, 3.5- and 2.8-fold higher than for non-residualizing iodinated IgG on days 3, 7 and 14, resp. Similar results were obtained for DLT-labeled IgG and fragments with residualized radiolabels. Tumor/organ ratios also were higher with residualizing labels. No significant differences in tumor, blood and organ uptake were observed between murine and humanized LL2. The conventionally iodinated anti-CD20 antibody, 1F5, had tumor uptake values comparable to those of iodinated LL2, the uptake of both antibodies being strongly dependent on tumor size. These data suggest that, with internalizing antibodies such as LL2, labeling with intracellularly retained isotopes has an advantage over released ones, which justifies further clin. trials with residualizing ¹¹¹In-labeled LL2 for diagnosis, and residualizing ¹³¹I and ⁹⁰Y labels for therapy.

L4 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:333908 HCAPLUS

DOCUMENT NUMBER: 127:2536

TITLE: The advantage of residualizing radiolabels for targeting B-cell lymphomas with a radiolabeled anti-CD22 monoclonal antibody

AUTHOR(S): Mattes, M. Jules; Shih, Lisa B.; Govindan, Serengulam V.; Sharkey, Robert M.; Ong, Gaik Lin; Xuan, Hong; Goldenberg, David M.

CORPORATE SOURCE: Garden State Cancer Center at the Center for Molecular Medicine and Immunology, Belleville, NJ, 07109, USA

SOURCE: International Journal of Cancer (1997), 71(3), 429-435
 CODEN: IJCNAW; ISSN: 0020-7136

PUBLISHER: Wiley-Liss

DOCUMENT TYPE: Journal

LANGUAGE: English

AB CD22 antibodies (Abs) bound to B-cell lymphomas are known to be internalized and catabolized rapidly. Therefore, it would be expected that use of CD22 as a target for

radioimmunotherapy should be enhanced by the use of "residualizing" radiolabels, which are trapped within the cell after catabolism of the Ab to which they had been conjugated. Our study was intended to evaluate this hypothesis using Ab LL2. In initial expts., we found that LL2 binding was strongly temperature dependent, with approx. 15-fold greater binding at 37°C than at 0°C. A series of expts. suggested that this difference is due to a conformational change in the antigen at low temperature, so that the LL2 epitope is partially blocked. In vitro, residualizing labels-including 125I-dilactitol tyramine and 111In-DTPA-were retained by cells much longer than a conventional iodine label. In vivo, residualizing labels also showed a marked advantage in terms of uptake by Ramos **B-cell** lymphoma xenografts in nude mice. However, the absolute Ab uptake by xenografts was quite low, in comparison with results obtained with many carcinoma xenografts, which appears to be due in part to vascular properties of the **B-cell** lymphoma xenografts.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:162203 HCPLUS

DOCUMENT NUMBER: 124:229437

TITLE: Construction and characterization of a humanized, internalizing, **B-cell** (CD22)-specific, leukemia/lymphoma antibody, LL2

AUTHOR(S): Leung, Shui-On; **Goldenberg, David M.**; Dion, Arnold S.; Pellegrini, Matthew C.; Shevitz, Jerry; Shih, Lisa B.; Hansen, Hans J.

CORPORATE SOURCE: Immunomedics, Inc., Morris Plains, NJ, 07950, USA
SOURCE: Molecular Immunology (1995), 32(17/18), 1413-27

CODEN: MOIMD5; ISSN: 0161-5890

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The murine monoclonal antibody, LL2, is a **B-cell** (CD22)-specific IgG2a which has been demonstrated to be clin. significant in the radioimmunodetection of non-Hodgkin's **B-cell** lymphoma. The antibody carries a variable region-appended glycosylation site in the light chain, and is rapidly internalized upon binding to Raji target cells. Humanization of LL2 was carried out in order to develop LL2 as a diagnostic and **immunotherapeutic** suitable for repeated administration. Based on the extent of sequence homol., and with the aid of computer modeling, we selected the EU framework regions (FR) 1, 2 and 3, and the NEWM FR4 as the scaffold for grafting the heavy chain complementarity determining regions (CDRs), and the

REI

FRs for that of light chains. The light chain glycosylation site, however, was not included. Construction of the CDR-grafted variable regions was accomplished by a rapid and simplified method that involved long DNA oligonucleotide synthesis and the polymerase chain reaction (PCR). The humanized LL2 (hLL2), lacking light chain variable region glycosylation, exhibited immunoreactivities that were comparable to that of chimeric LL2 (cLL2), which was shown previously to have antigen-binding properties similar to its murine counterpart, suggesting that the VK-appended oligosaccharides found in mLL2 are not necessary for antigen binding. Moreover, the hLL2 retained its ability to be internalized into Raji cells at a rate similar to its murine and chimeric counterparts.

L4 ANSWER 17 OF 17 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:321048 HCAPLUS
DOCUMENT NUMBER: 120:321048
TITLE: Internalization and intracellular processing of an anti-B-cell lymphoma monoclonal antibody, LL2
AUTHOR(S): Shih, Lisa B.; Lu, Helen H. Z.; Xuan, Hong; Goldenberg, David M.
CORPORATE SOURCE: Garden State Cancer Cent., Cent. Mol. Med. Immunol., Newark, NJ, 07103, USA
SOURCE: International Journal of Cancer (1994), 56(4), 538-45
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The successful clin. experience with antibody LL2 (an IgG2a, anti-B-cell lymphoma antibody) in radioimmunodetection and **radioimmunotherapy** suggests that this antibody may have potential as a carrier of cytotoxic agents. The internalization, cellular trafficking, and catabolism of this antibody in target human Burkitt lymphoma cells (Raji) were investigated. Internalization of intact antibody as well as of the F(ab')2 and Fab' fragments was detected by an FITC-labeled anti-mouse second antibody probe, and evaluated by fluorescence microscopy. Internalization of intact IgG (or the fragments) was observed as early as 5 min after incubation at 37°. Initially, the internalized antibodies were present as micro-particles inside the cell membrane, and were translocated to the lysosomal compartment within 2 h. The anat. location of the internalized antibody, before translocation to the lysosomal compartment, was deduced by comparing the fluorescence images obtained with the antibody to those obtained with fluorescent probes with known cellular distribution in a co-internalization study. A Golgi-like compartment was found to be involved in the translocation of the antibody. Cellular catabolism of the bound antibody was studied by using ¹²⁵I-labeled antibody on the target cells. At 21 h, 40% of the radioactivity was released into the supernatant as degraded fragments. The observation suggested that the antibody was degraded mainly in the lysosomes, since the degradation was significantly inhibited in the presence of lysosomal inhibitors such as ammonium chloride or leupeptin. Subcellular fractionation of Raji cells after the binding of ¹²⁵I-labeled LL2 indicated that the antibody was translocated to lysosomes as evidenced by SDS-PAGE. The rate of internalization (Ke) of LL2, and the re-expression of the antigen were determined. The rapid internalization of LL2 and the re-expression of the antigen suggest that this antibody may have potential as a therapeutic immunoconjugate, since it could deliver a higher accumulation of cytotoxic agents into lymphoma cells.

=> d que stat 126

L1 43 SEA FILE=HCAPLUS ABB=ON ?ANTI? (W) ?CD22? (W) ?ANTIBOD?

L2 37 SEA FILE=HCAPLUS ABB=ON L1 AND (?HUMAN? OR ?CHIMER?)

L3 1 SEA FILE=REGISTRY ABB=ON BORON/CN

L4 21 SEA FILE=HCAPLUS ABB=ON L2 AND (L3 OR ?DRUG? OR ?TOXIN? OR
?IMMUNOMODULAT? OR ?CHELAT? OR ?BORON? OR ?PHOTOACT? (W) (?AGENT?
OR DYE?) OR ?RADIOISOTOP?)

L6 1 SEA FILE=REGISTRY ABB=ON IODINE/CN

L7 3 SEA FILE=HCAPLUS ABB=ON L4 AND (L6 OR ?IODIN?)

L8 21 SEA FILE=HCAPLUS ABB=ON L4 OR L7

L12 6 SEA FILE=HCAPLUS ABB=ON L8 AND (CYCLOPHOSPHAMIDE OR ETOPOSIDE
OR VINCRISTINE OR PROCARBAZINE OR PREDNISONE OR CARMUSTINE OR
DOXORUBICIN OR METHOTREXATE OR BLEOMYCIN OR DEXAMETHASONE OR
PHENYL BUTYRATE OR BRYOSTATIN-1 OR LEUCOVORIN)

L13 2 SEA FILE=REGISTRY ABB=ON (NITROGEN MUSTARD OR NITROSOUreas OR
TRIAZENES OR FOLIC ACID ANALOGS OR PYRIMIDINE ANALOGS OR
PURINE ANALOGS OR EPIPODOPHYLLOTOXINS OR PLATINUM OR HORMONES) /
CN

L14 3 SEA FILE=HCAPLUS ABB=ON L8 AND (L13 OR NITROGEN MUSTARD OR
NITROSOUreas OR TRIAZENES OR FOLIC ACID ANALOGS OR PYRIMIDINE
ANALOGS OR PURINE ANALOGS OR EPIPODOPHYLLOTOXINS OR PLATINUM (W)
?COORD? (W) ?COMPOUND? OR HORMONES)

L15 4 SEA FILE=REGISTRY ABB=ON (RICIN OR ABRIN OR RIBONUCLEASE OR
DNASE 1 OR STAPHYLOCOCCAL ENTEROTOXIN-A OR POKEWEED ANTIVIRAL
PROTEIN OR GELONIN OR DIPHTHERIN TOXIN OR PSEUDOMONAS EXOTOXIN
OR PSEUDOMONAS ENDOTOXIN) /CN

L16 13 SEA FILE=HCAPLUS ABB=ON L8 AND (L15 OR RICIN OR ABRIN OR
RIBONUCLEASE OR DNASE 1 OR STAPHYLOCOCCAL ENTEROTOXIN-A OR
POKEWEED ANTIVIRAL PROTEIN OR GELONIN OR DIPHTHERIN TOXIN OR
PSEUDOMONAS EXOTOXIN OR PSEUDOMONAS ENDOTOXIN)

L17 21 SEA FILE=HCAPLUS ABB=ON L4 OR L12 OR L14 OR L16

L18 3 SEA FILE=REGISTRY ABB=ON (G-CSF OR GM-CSF OR THROMBOPOIETIN
OR IL-1 OR IL-3 OR IL-12) /CN

L19 5 SEA FILE=HCAPLUS ABB=ON L17 AND (L18 OR IL 1 OR IL 2 OR IL
12)

L20 3 SEA FILE=REGISTRY ABB=ON (CD 9 OR CD 20 OR CD 52 OR CD 74) /CN

L23 6 SEA FILE=HCAPLUS ABB=ON L17 AND (L20 OR CD9 OR CD20 OR CD52
OR CD74)

L25 6 SEA FILE=HCAPLUS ABB=ON L17 AND (L19 OR L23 OR P-BROMOACETAMID
O-BENZYL-TETRAETHYLAMINETETRACETIC ACID)

L26 21 SEA FILE=HCAPLUS ABB=ON L17 OR L19 OR L23 OR L25

=> d ibib abs 126 1-21

L26 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:808917 HCAPLUS
 TITLE: Cell surface sialic acids do not affect primary CD22
interactions with CD45 and surface IgM nor the rate of
constitutive CD22 endocytosis
 AUTHOR(S): Zhang, Mai; Varki, Ajit
 CORPORATE SOURCE: Glycobiology Research and Training Center, Departments
of Medicine and Cellular and Molecular Medicine,
School of Medicine, University of California, San
Diego, La Jolla, CA, 92093-0687, USA
 SOURCE: Glycobiology (2004), 14(11), 939-949
 CODEN: GLYCE3; ISSN: 0959-6658
 PUBLISHER: Oxford University Press
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB CD22/Siglec-2 is a B cell-specific mol. modulating surface IgM (sIgM) signaling via cytosolic tyrosine-based motifs. CD22 recognizes α 2-6-linked sialic acids (Sias) via an amino-terminal Ig-like domain. This Sia-binding site is typically masked by unknown sialylated ligands on the same cell surface, an interaction required for optimal signaling function. We studied the effect of cell surface Sias on specific interactions of CD22 with other mols. and on its turnover via endocytosis. A novel approach for simultaneous biotinylation and crosslinking showed that CD22 assocs. with CD45 and sIgM at much higher levels than reported in prior studies, possibly involving cell surface multimers of CD22. Sia removal or mutation of a CD22 arginine residue required for Sia recognition did not affect these assocns. even in human:mouse heterologous systems, indicating that they are primarily determined by evolutionarily conserved protein-protein interactions. Thus masking of the Sia-binding site of CD22 involves many cell surface sialoglycoproteins, without requiring specific ligand(s) and/or is mediated by secondary interactions with Sias on CD45 and sIgM. Abrogating Sia interactions also does not affect constitutive CD22 endocytosis. Sia removal does enhance the much faster rate of anti-CD22 antibody-triggered endocytosis, as well as killing by an anti-CD22 immunotoxin. In contrast to the unstimulated state, sIgM crosslinking inhibits both antibody-induced endocytosis and immunotoxin killing. Thus the signal-modulating activity of CD22 Sia recognition cannot be explained by mediation of primary interactions with specific mols., nor by effects on constitutive endocytosis. The effects on antibody-mediated endocytosis could be of relevance to immunotoxin treatment of lymphomas.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:802607 HCAPLUS

DOCUMENT NUMBER: 141:312949

TITLE: Anti-CD22 antibodies

conjugated with cytotoxic drug for treating cancer, carcinoma, sarcoma and B cell lymphoma/leukemia

INVENTOR(S): Kunz, Arthur; Moran, Justin Keith; Rubino, Joseph Thomas; Jain, Neera; Vidunas, Eugene Joseph; Simpson, John McLean; Merchant, Nishith; Dijoseph, John Francis; Ruppen, Mark Edward; Damle, Nitin Krishnaji; Robbins, Paul David; Popplewell, Andrew George

PATENT ASSIGNEE(S): Wyeth Holdings Corporation, USA

SOURCE: U.S. Pat. Appl. Publ., 90 pp., Cont.-in-part of U.S. Ser. No. 428,894.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
US 2004192900	A1	20040930	US 2003-699874	20031103
US 2004082764	A1	20040429	US 2003-428894	20030502
PRIORITY APPLN. INFO.:			US 2002-377440P	P 20020502
			US 2003-428894	A2 20030502

AB Methods for preparing monomeric cytotoxic drug/carrier conjugates with a drug loading significantly higher than in previously reported procedures and with decreased aggregation and low conjugate

fraction (LCF) are described. Cytotoxic drug derivative/antibody conjugates, compns. comprising the conjugates and uses of the conjugates are also described. Monomeric calicheamicin derivative/anti-CD22 antibody conjugates, compns. comprising the conjugates and uses of the conjugates are also described. The anti-CD22 antibody is a monoclonal antibody, human antibody, chimeric antibody, humanized antibody or fragment. The cytotoxic drug is a calicheamicin, thiotapec, taxane, vincristine, daunorubicin, doxorubicin, epirubicin, esperamicin, actinomycin, anthramycin, azaserine, bleomycin, tamoxifen, idarubicin, etc.

L26 ANSWER 3 OF 21 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:302727 HCPLUS

DOCUMENT NUMBER: 140:399509

TITLE: Induction of caspase-dependent programmed cell death in B-cell chronic lymphocytic leukemia by anti-CD22 immunotoxins

AUTHOR(S): Decker, Thomas; Oelsner, Madlene; Kreitman, Robert J.; Salvatore, Giuliana; Wang, Qing-cheng; Pastan, Ira; Peschel, Christian; Licht, Thomas

CORPORATE SOURCE: III. Medizinische Klinik, Klinikum rechts der Isar, Technische Universitaet Muenchen, Munich, 81675, Germany

SOURCE: Blood (2004), 103(7), 2718-2726

CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB B cells of chronic lymphocytic leukemia (CLL) are long-lived *in vivo*, possibly because of defects in apoptosis. The authors investigated BL22, an immunotoxin composed of the Fv portion of an anti-CD22 antibody fused to a 38-kDa *Pseudomonas* exotoxin-A fragment. B cells from 22 patients with CLL were immunomagnetically enriched (96% purity) and were cultured with BL22 or an immunotoxin that does not recognize hematopoietic cells. The antileukemic activity of BL22 was correlated with CD22 expression, as determined by flow cytometry. BL22 induced caspase-9 and caspase-3 activation, poly(ADP [ADP]-ribose)polymerase (PARP) cleavage, DNA fragmentation, and membrane flipping. Cell death was associated with the loss of mitochondrial membrane potential and the down-regulation of Mcl-1 and X-chromosomal inhibitor of apoptosis protein (XIAP). Furthermore, BL22 induced a proapoptotic 18-kDa Bax protein and conformational changes of Bax. ZVAD.fmk abrogated apoptosis, confirming that cell death was executed by caspases. Conversely, interleukin-4, a survival factor, inhibited spontaneous death in culture but failed to prevent immunotoxin-induced apoptosis. BL22 cytotoxicity was markedly enhanced when combined with anticancer drugs including vincristine. The authors also investigated HA22, a newly engineered immunotoxin, in which BL22 residues are mutated to improve target binding. HA22 was more active than BL22. These immunotoxins thus induce caspase-mediated apoptosis involving mitochondrial damage. Combination with chemotherapy is expected to improve the efficacy of immunotoxin treatment.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 4 OF 21 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:991654 HCPLUS

DOCUMENT NUMBER: 140:40893

TITLE: Novel stable anti-CD22
 antibodies derived from monoclonal antibody
 LL2 for diagnosis and therapy of B cell lymphoma or B
 cell non-Hodgkin's lymphoma
 INVENTOR(S): Rybak, Susanna; Arndt, Michaela; Krauss, Jurgen
 PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
 SOURCE: PCT Int. Appl., 66 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003104425	A2	20031218	WO 2003-US18201	20030609
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2002-387306P P 20020607

AB The present invention provides stable anti-CD22
 antibodies, nucleic acids encoding stable anti-
 CD22 antibodies, and therapeutic and diagnostic methods
 and compns. using stable anti-CD22 antibodies
 . These humanized scFv fragment variants are derived from
 murine monoclonal anti-human CD22 antibody LL2, and are useful
 for detecting CD22-expressing mammalian or human cells, and
 diagnosis and therapy of B cell lymphoma or B cell non-Hodgkin's lymphoma.

L26 ANSWER 5 OF 21 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:892567 HCPLUS
 DOCUMENT NUMBER: 139:386334
 TITLE: Production of monomeric calicheamicin derivative
 cytotoxic drug/carrier conjugates
 INVENTOR(S): Kunz, Arthur; Moran, Justin Keith; Rubino, Joseph
 Thomas; Jain, Neera; Vidunas, Eugene Joseph; Simpson,
 John McLean; Robbins, Paul David; Merchant, Nishith;
 Dijoseph; John Francis; Ruppen, Mark Edward; Damle,
 Nitin Krishnaji; Popplewell, Andrew George; et al.
 PATENT ASSIGNEE(S): Wyeth Holdings Corporation, USA
 SOURCE: PCT Int. Appl., 186 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003092623	A2	20031113	WO 2003-US13910	20030502
WO 2003092623	A3	20040318		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
 PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
 TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-377440P P 20020502

AB The present invention relates to methods for the production of monomeric cytotoxic drug/carrier conjugates (the "conjugates") with higher drug loading and substantially reduced low conjugate fraction (LCF). Cytotoxic drug derivative/antibody conjugates, compns. comprising the conjugates and uses of the conjugates are also described. Particularly, the invention relates to anti-CD22 antibody-monomeric calicheamicin conjugates. The invention also relates to the conjugates of the invention, to methods of purification of the conjugates, to pharmaceutical compns. comprising the conjugates, and to uses of the conjugates.

L26 ANSWER 6 OF 21 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:494161 HCPLUS

DOCUMENT NUMBER: 139:190449

TITLE: Current treatment strategies for patients with hairy cell leukemia

AUTHOR(S): Tallman, Martin S.

CORPORATE SOURCE: Robert H. Lurie Comprehensive Cancer Center,
 Northwestern University Feinberg School of Medicine,
 Chicago, IL, USA

SOURCE: Reviews in Clinical and Experimental Hematology
 (2002), 6(4), 389-400

PUBLISHER: CODEN: RCEHFB; ISSN: 1127-0020
 Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Hairy cell leukemia is uncommon, but recent developments in treatment have improved the outcome. Splenectomy was the preferred treatment for many years until the efficacy of interferon was clearly demonstrated. Currently, the purine analogs have emerged as the treatments of choice. 2-Chlorodeoxyadenosine (2-CdA) is resistant to the action of adenosine deaminase. Since this agent generally is administered as a single 7-day course with a paucity of toxicities, many investigators have suggested it is the preferable agent. However, the outcome associated with 2-CdA has never been compared to 2-deoxycoformycin in a prospective randomized trial. Therefore, it is not known whether one or the other agent is associated with improved long-term outcome. The new immunotoxin, BL22, which is a fusion of an anti-CD22 antibody linked to a portion of the *Pseudomonas exotoxin A*, has proved to be very effective for patients who have failed or are refractory to the purine analogs. The role of this agent as initial therapy for newly diagnosed patients has not been explored.

REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 7 OF 21 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:379520 HCPLUS

DOCUMENT NUMBER: 139:99486

TITLE: CD22 as a target of passive immunotherapy

AUTHOR(S): Cesano, Alessandra; Gayko, Urte

CORPORATE SOURCE: Amgen Inc., Thousand Oaks, CA, USA
 SOURCE: Seminars in Oncology (2003), 30(2), 253-257
 CODEN: SOLGAV; ISSN: 0093-7754

PUBLISHER: W. B. Saunders Co.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. CD22 is a 135 kDa B-cell restricted sialoglycoprotein present in the cytoplasm of virtually all B-lineage cells but expressed on the B-cell surface only at mature stages of differentiation. In humans, the vast majority of IgM+ IgD+ B cells express cell-surface CD22, while in lymphoid tissues CD22 expression is high in follicular mantle and marginal zone B cells and weak in germinal center B cells. In B-cell malignancies, CD22 expression ranges from 60% to 80% depending on the histol. type and on the assays used. The function of the CD22 mol. is uncertain, although recent studies have suggested roles for the mol. both as a component of the B-cell activation complex and as an adhesion mol. CD22-deficient mice have a reduced number of mature B cells in the bone marrow and circulation; the B cells have a shorter lifespan and enhanced apoptosis, thus indicating a key role of this antigen in B-cell development/survival. After binding with its natural ligand(s) or antibodies, CD22 is rapidly internalized; this provides a potent costimulatory signal in primary B-cell and proapoptotic signals in neoplastic B cells. Preclinically CD22 has been shown to be an effective target for immunotherapy of B-cell malignancies using either "naked" or toxin-labeled or radiolabeled monoclonal antibodies. Clin. trials in patients with non-Hodgkin's lymphoma (NHL) (both indolent and aggressive disease) are now ongoing with a **humanized naked anti-CD22 antibody** (epratuzumab, Amgen Inc, thousand Oaks, CA and Immunomedics Inc, Morris Plains, NJ) used as single agent or in combination with other monoclonal antibodies (ie, rituximab) and/or chemotherapy. Preliminary data from these studies showed these approaches to be effective and well-tolerated.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:261860 HCAPLUS

DOCUMENT NUMBER: 138:286011

TITLE: Mutated anti-CD22

antibodies and their immunoconjugates or immunotoxins for treating leukemia and lymphoma expressing CD22

INVENTOR(S): Pastan, Ira H.; Salvatore, Giuliana; Beers, Richard; Kreitman, Robert J.

PATENT ASSIGNEE(S): The Government of the United States, as Represented by the Secretary of Health and Human Services, USA

SOURCE: PCT Int. Appl., 59 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003027135	A2	20030403	WO 2002-US30316	20020925
WO 2003027135	A3	20040311		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,			

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
 PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
 UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
 CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1448584 A2 20040825 EP 2002-761818 20020925

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.: US 2001-325360P P 20010926
 WO 2002-US30316 W 20020925

AB Recombinant **immunotoxins** are fusion proteins composed of the Fv domains of antibodies (i.e. RFB4) fused to bacterial or plant **toxins**. RFB4 (Fv)-PE38 is an **immunotoxin** that targets CD22 expressed on B cells and B cell malignancies. The present invention provides antibodies and antibody fragments that have improved ability to bind the CD22 antigen of B cells and B cell malignancies compared to RFB4. **Immunotoxins** made with the antibodies and antibody fragments of the invention have improved cytotoxicity to CD22-expressing cancer cells. Compns. that incorporate these antibodies into **chimeric immunotoxin** mols. that can be used in medicaments and methods for inhibiting the growth and proliferation of leukemia and lymphoma cells.

L26 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:979773 HCAPLUS

DOCUMENT NUMBER: 138:52028

TITLE: 131I-Labelled anti-CD22 MAb (LL2) in patients with B-cell lymphomas failing chemotherapy: Treatment outcome, haematological toxicity and bone marrow absorbed dose estimates

AUTHOR(S): Linden, Ola; Tennvall, Jan; Hindorf, Cecilia;
 Cavallin-Stahl, Eva; Lindner, Karl-Johan; Ohlsson, Tomas; Wingardh, Karin; Strand, Sven-Erik

CORPORATE SOURCE: Department of Oncology, Lund University Hospital, Lund, Swed.

SOURCE: Acta Oncologica (2002), 41(3), 297-303

PUBLISHER: CODEN: ACTOEL; ISSN: 0284-186X

DOCUMENT TYPE: Taylor & Francis Ltd.

LANGUAGE: English

AB The experience with radioimmunotherapy in B-cell lymphomas using the rapidly internalizing antibody, anti-CD22 (LL2), is limited. In this study we investigated the efficacy and toxicity of 131I-labeled-LL2 for radioimmunotherapy in patients with B-cell lymphomas that failed one or two cytostatic regimens. Eleven patients were treated with one or repeated cycles of 131I-anti-CD22 antibody, 1330 MBq/m² (36 mCi/m²). Six of the 11 treated patients demonstrated an objective response, three of them with complete remission. All follicular (3 patients) and transformed lymphomas (2 patients) responded compared to one of four diffuse large B-cell lymphomas. Two out of six responders exhibited event-free survival (EFS), which was comparable with or longer than the EFS following primary anthracycline-containing chemotherapy. Non-hematol. toxicity was mild. Hematol. toxicity was associated with pretreatment clin. characteristics but not with estimated absorbed bone marrow doses. Objective remission following treatment with 131I-anti-CD22 can be achieved in patients with various subtypes of B-cell lymphomas, failing standard chemotherapy. Follicular or transformed lymphomas seem particularly responsive. Hematol. toxicity seems to be dependent on the functional status of the bone marrow before radioimmunotherapy.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:586840 HCAPLUS
 DOCUMENT NUMBER: 138:162746
 TITLE: Technology evaluation: BL22, NCI
 AUTHOR(S): Barth, Stefan
 CORPORATE SOURCE: Institute of Biology, Aachen, 52074, Germany
 SOURCE: Current Opinion in Molecular Therapeutics (2002), 4 (1), 72-75
 CODEN: CUOTFO; ISSN: 1464-8431
 PUBLISHER: PharmaPress Ltd.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. BL22 (RFB4(dsFv)-PE38) is a recombinant **Pseudomonas exotoxin-based immunotoxin** under development by the National Cancer Institute for the treatment of B-cell malignancies. It is composed of the disulfide-stabilized Fv portion of the anti-CD22 antibody RFB4 genetically fused to a truncated form of **Pseudomonas exotoxin A**. It has entered phase I trials for the treatment of B-cell lymphoma.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:921712 HCAPLUS
 DOCUMENT NUMBER: 136:384477
 TITLE: Antibody targeted therapeutics for lymphoma: New focus on the CD22 antigen and RNA
 AUTHOR(S): Newton, Dianne L.; Rybak, Susanna M.
 CORPORATE SOURCE: SAIC Frederick and Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD, 21702, USA
 SOURCE: Expert Opinion on Biological Therapy (2001), 1(6), 995-1003
 CODEN: EOBTAA; ISSN: 1471-2598
 PUBLISHER: Ashley Publications Ltd.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. The approval of antibodies for cancer treatment has provoked increased interest in the development of new and improved antibody-mediated therapies. This emerging approach centers on targeting CD22 on **human** B-cells with a monoclonal antibody (mAb). **Anti-CD22 antibodies conjugated to a cytotoxic RNase** elicits potent and specific killing of the lymphoma cells in vitro and in **human** lymphoma models in severe combined immune deficiency (SCID) mice. RNA damage caused by RNases could be an important alternative to standard DNA damaging chemotherapeutics. Moreover, targeted RNases may overcome problems of toxicity and immunogenicity associated with plant- or bacterial **toxin-containing immunotoxins**.

REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:771011 HCAPLUS
 DOCUMENT NUMBER: 135:317474
 TITLE: Immunotherapy of B-cell malignancies using

anti-CD22 antibodies

INVENTOR(S) : Goldenberg, David M.
 PATENT ASSIGNEE(S) : Immunomedics, Inc., USA
 SOURCE: U.S., 14 pp., Cont.-in-part of U.S. 6,183,744.
 CODEN: USXXAM

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6306393	B1	20011023	US 1999-307816	19990510
EP 1431311	A1	20040623	EP 2004-75775	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1459768	A2	20040922	EP 2004-75774	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CA 2373618	AA	20001116	CA 2000-2373618	20000510
WO 2000067795	A1	20001116	WO 2000-US12583	20000510
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2000048296	A5	20001121	AU 2000-48296	20000510
AU 774044	B2	20040617		
EP 1178826	A1	20020213	EP 2000-930484	20000510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002544173	T2	20021224	JP 2000-616820	20000510
US 2002041847	A1	20020411	US 2001-921290	20010803
US 2002071807	A1	20020613	US 2001-965796	20011001
US 2003124058	A1	20030703	US 2002-314330	20021209
US 2004219203	A1	20041104	US 2003-706852	20031112
PRIORITY APPLN. INFO.:			US 1997-41506P	P 19970324
			US 1998-38995	A2 19980312
			EP 1998-912936	A3 19980317
			US 1999-307816	A 19990510
			WO 2000-US12583	W 20000510
			US 2000-590284	A1 20000609
			US 2001-965796	A1 20011001
			US 2002-360259P	P 20020301
			US 2002-314330	A2 20021209
			US 2003-350096	A2 20030124
			US 2003-377122	A2 20030303
			US 2003-478830P	P 20030617

AB B-cell malignancies, such as the B-cell subtype of non-Hodgkin's lymphoma and chronic lymphocytic leukemia, are significant contributors to cancer mortality. The response of B-cell malignancies to various forms of treatment is mixed. Traditional methods of treating B-cell malignancies, including chemotherapy and radiotherapy, have limited utility due to toxic side effects. Immunotherapy with anti-CD20 antibodies have also provided limited success. The use of antibodies that bind with the CD22 or CD19 antigen, however, provides an effective means to treat B-cell

malignancies such as indolent and aggressive forms of B-cell lymphomas, and acute and chronic forms of lymphatic leukemias. Moreover, immunotherapy with anti-CD22 and/or anti-CD19 antibodies requires comparatively low doses of antibody protein, and can be used effectively in multimodal therapies.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 13 OF 21 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:814346 HCPLUS

DOCUMENT NUMBER: 133:361914

TITLE: Immunotherapy of B-cell malignancies using anti-CD22 antibodies

INVENTOR(S): Goldenberg, David M.

PATENT ASSIGNEE(S): Immunomedics, Inc., USA

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067795	A1	20001116	WO 2000-US12583	20000510
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6306393	B1	20011023	US 1999-307816	19990510
CA 2373618	AA	20001116	CA 2000-2373618	20000510
AU 2000048296	A5	20001121	AU 2000-48296	20000510
AU 774044	B2	20040617		
EP 1178826	A1	20020213	EP 2000-930484	20000510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002544173	T2	20021224	JP 2000-616820	20000510
PRIORITY APPLN. INFO.:			US 1999-307816	A2 19990510
			US 1997-41506P	P 19970324
			US 1998-38995	A2 19980312
			WO 2000-US12583	W 20000510

AB B-cell malignancies, such as the B-cell subtype of non-Hodgkin's lymphoma and chronic lymphocytic leukemia, are significant contributors to cancer mortality. The response of B-cell malignancies to various forms of treatment is mixed. Traditional methods of treating B-cell malignancies, including chemotherapy and radiotherapy, have limited utility due to toxic side effects. Immunotherapy with anti-CD20 antibodies have also provided limited success. The use of antibodies that bind with the CD22 or CD19 antigen, however, provides an effective means to treat B-cell malignancies such as indolent and aggressive forms of B-cell lymphomas, and acute and chronic forms of lymphatic leukemias. Moreover, immunotherapy with anti-CD22 and/or anti-CD19 antibodies requires comparatively low doses of antibody protein, and can be used effectively in multimodal therapies.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1999:186813 HCAPLUS
 DOCUMENT NUMBER: 131:27541
 TITLE: Complete regression of **human** B-cell lymphoma
 xenografts in mice treated with recombinant anti-CD22
immunotoxin RFB4(dsFv)-PE38 at doses tolerated
 by cynomolgus monkeys
 AUTHOR(S): Kreitman, Robert J.; Wang, Qing-Cheng; FitzGerald,
 David J. P.; Pastan, Ira
 CORPORATE SOURCE: Laboratory of Molecular Biology, Division of Basic
 Sciences, National Cancer Institute, National
 Institutes of Health, Bethesda, MD, 20892, USA
 SOURCE: International Journal of Cancer (1999), 81(1), 148-155
 CODEN: IJCAW; ISSN: 0020-7136
 PUBLISHER: Wiley-Liss, Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB RFB4(dsFv)-PE38 is a recombinant **immunotoxin** in which the
 variable light domain (VL) is disulfide bonded via cysteine residues to
 the variable heavy domain (VH), which in turn is fused to PE38, a mutant
 form of **Pseudomonas exotoxin** A. RFB4 binds to CD22,
 which is a differentiation antigen expressed on the majority of B-cell
 leukemias and lymphomas. To examine the potential efficacy of
 RFB4(dsFv)-PE38 when administered at a dose schedule appropriate for phase
 I testing, mice bearing CA46 **human** CD22+ Burkitt's lymphoma
 xenografts were treated on alternate days i.v. for 3 doses (QOD +3).
 Complete regressions were observed in 80% and 100% of mice treated with 200
 and 275 µg/kg QOD +3, resp. The higher dose was 27% of the LD50
 and 34% of the LD10 in mice. Because RFB4(dsFv)-PE38 is stable at
 37°, it could also be given by continuous infusion using pumps
 placed in the peritoneal cavity; complete regressions also resulted from
 this mode of administration. To study toxicol., a pilot toxicol. study of
 RFB4(dsFv)-PE38 was undertaken in cynomolgus monkeys, which like
humans but unlike mice have CD22, which binds RFB4. Doses of 100
 and 500 µg/kg i.v. QOD +3 were well tolerated, indicating that a
 dose that cured tumors in mice was tolerated by primates. Based on these
 preclin. results, RFB4(dsFv)-PE38 is being developed for the treatment of
 patients with CD22-pos. leukemias and lymphomas.
 REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1998:745101 HCAPLUS
 DOCUMENT NUMBER: 130:13215
 TITLE: Onconase **immunotoxins** directed against
 malignant B-cells
 INVENTOR(S): Rybak, Susanna M.; Newton, Dianne L.; Goldenberg,
 David M.
 PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA;
 Immunomedics, Inc.
 SOURCE: PCT Int. Appl., 54 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
------------	------	------	-----------------	------

WO 9850435	A1	19981112	WO 1998-US8983	19980501
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
CA 2288232	AA	19981112	CA 1998-2288232	19980501
AU 9872803	A1	19981127	AU 1998-72803	19980501
AU 745823	B2	20020411		
EP 975674	A1	20000202	EP 1998-920171	19980501
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
JP 2001507944	T2	20010619	JP 1998-548301	19980501
JP 2004115529	A2	20040415	JP 2003-362606	20031022
PRIORITY APPLN. INFO.:				
			US 1997-46895P	P 19970502
			JP 1998-548301	A3 19980501
			WO 1998-US8983	W 19980501

AB The authors disclose **immunotoxins** that effectively kill malignant B-cells having the surface marker CD22. The antibody portion of these reagents are chemical conjugated or recombinantly fused to the **RNase A homolog (onconase)** derived from *Rana pipiens*. In addition, onconase **immunotoxins** may be prepared from antibodies directed to **CD74** wherein their therapeutic application may be extended to include neuroblastoma and melanoma.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 16 OF 21 HCPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:661515 HCPLUS

DOCUMENT NUMBER: 129:274703

TITLE: Immunotherapy of B-cell malignancies using anti-CD22 antibodies

INVENTOR(S): Goldenberg, David M.

PATENT ASSIGNEE(S): IMMUNOMEDICS, INC., USA

SOURCE: PCT Int. Appl., 41 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9842378	A1	19981001	WO 1998-US5075	19980317
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
US 6183744	B1	20010206	US 1998-38955	19980312
CA 2284829	AA	19981001	CA 1998-2284829	19980317
AU 9867610	A1	19981020	AU 1998-67610	19980317
AU 728325	B2	20010104		

=> d que stat 128

L1 43 SEA FILE=HCAPLUS ABB=ON ?ANTI? (W) ?CD22? (W) ?ANTIBOD?

L2 37 SEA FILE=HCAPLUS ABB=ON L1 AND (?HUMAN? OR ?CHIMER?)

L3 1 SEA FILE=REGISTRY ABB=ON BORON/CN

L4 21 SEA FILE=HCAPLUS ABB=ON L2 AND (L3 OR ?DRUG? OR ?TOXIN? OR
?IMMUNOMODULAT? OR ?CHELAT? OR ?BORON? OR ?PHOTOACT? (W) (?AGENT?
OR DYE?) OR ?RADIOISOTOP?)

L6 1 SEA FILE=REGISTRY ABB=ON IODINE/CN

L7 3 SEA FILE=HCAPLUS ABB=ON L4 AND (L6 OR ?IODIN?)

L8 21 SEA FILE=HCAPLUS ABB=ON L4 OR L7

L12 6 SEA FILE=HCAPLUS ABB=ON L8 AND (CYCLOPHOSPHAMIDE OR ETOPOSIDE
OR VINCRISTINE OR PROCARBAZINE OR PREDNISONE OR CARMUSTINE OR
DOXORUBICIN OR METHOTREXATE OR BLEOMYCIN OR DEXAMETHASONE OR
PHENYL BUTYRATE OR BRYOSTATIN-1 OR LEUCOVORIN)

L13 2 SEA FILE=REGISTRY ABB=ON (NITROGEN MUSTARD OR NITROSOUreas OR
TRIAZENES OR FOLIC ACID ANALOGS OR PYRIMIDINE ANALOGS OR
PURINE ANALOGS OR EPIPODOPHYLLOTOXINS OR PLATINUM OR HORMONES) /
CN

L14 3 SEA FILE=HCAPLUS ABB=ON L8 AND (L13 OR NITROGEN MUSTARD OR
NITROSOUreas OR TRIAZENES OR FOLIC ACID ANALOGS OR PYRIMIDINE
ANALOGS OR PURINE ANALOGS OR EPIPODOPHYLLOTOXINS OR PLATINUM (W)
?COORD? (W) ?COMPOUND? OR HORMONES)

L15 4 SEA FILE=REGISTRY ABB=ON (RICIN OR ABRIN OR RIBONUCLEASE OR
DNASE 1 OR STAPHYLOCOCCAL ENTEROTOXIN-A OR POKEWEED ANTIVIRAL
PROTEIN OR GELONIN OR DIPHTHERIN TOXIN OR PSEUDOMONAS EXOTOXIN
OR PSEUDOMONAS ENDOTOXIN) /CN

L16 13 SEA FILE=HCAPLUS ABB=ON L8 AND (L15 OR RICIN OR ABRIN OR
RIBONUCLEASE OR DNASE 1 OR STAPHYLOCOCCAL ENTEROTOXIN-A OR
POKEWEED ANTIVIRAL PROTEIN OR GELONIN OR DIPHTHERIN TOXIN OR
PSEUDOMONAS EXOTOXIN OR PSEUDOMONAS ENDOTOXIN)

L17 21 SEA FILE=HCAPLUS ABB=ON L4 OR L12 OR L14 OR L16

L27 48 SEA L17

L28 30 DUP REMOV L27 (18 DUPLICATES REMOVED)

=> d ibib abs 128 1-30

L28 ANSWER 1 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2004357819 EMBASE

TITLE: Epratuzumab, a **humanized anti-**
CD22 antibody, in aggressive
non-Hodgkin's lymphoma: Phase I/II clinical trial results.

AUTHOR: Leonard J.P.; Coleman M.; Ketas J.C.; Chadburn A.; Furman
R.; Schuster M.W.; Feldman E.J.; Ashe M.; Schuster S.J.;
Wegener W.A.; Hansen H.J.; Ziccardi H.; Eschenberg M.;
Gayko U.; Fields S.Z.; Cesano A.; Goldenberg D.M.

CORPORATE SOURCE: J.P. Leonard, Division of Hematology and Oncology, Weill
Med. Coll. of Cornell Univ., New York Presbyterian
Hospital, 520 East 70th Street, New York, NY 10021, United
States. jpleonar@med.cornell.edu

SOURCE: Clinical Cancer Research, (15 Aug 2004) 10/16 (5327-5334).
Refs: 55
ISSN: 1078-0432 CODEN: CCREF4

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Purpose: We conducted a single-center, dose-escalation study evaluating the safety, pharmacokinetics, and efficacy of epratuzumab, an anti-CD22 **humanized** monoclonal antibody, in patients with aggressive non-Hodgkin's lymphoma. Experimental Design: Epratuzumab was administered once weekly for 4 weeks at 120-1000-mg/m² doses to 56 patients [most (n = 35) with diffuse large B-cell lymphoma]. Results: Patients were heavily pretreated (median, 4 prior therapies), 25% received prior high-dose chemotherapy with stem cell transplant, and 84% had bulky disease (\geq 5 cm). Epratuzumab was well tolerated, with no dose-limiting toxicity. Most (95%) infusions were completed within 1 h. The mean serum half-life was 23.9 days. Across all dose levels and histologies, objective responses (ORs) were observed in five patients (10%; 95% confidence interval, 3-21%), including three complete responses. In patients with diffuse large B-cell lymphoma, 15% had ORs. Overall, 11 (20%) patients experienced some tumor mass reduction. Median duration of OR was 26.3 weeks, and median time to progression for responders was 35 weeks. Two responses are ongoing at \geq 34 months, including one rituximab-refractory patient. Conclusions: These data demonstrate that epratuzumab has a good safety profile and exerts antitumor activity in aggressive non-Hodgkin's lymphoma at doses of \geq 240 mg/m², thus warranting further evaluation in this clinical setting.

L28 ANSWER 2 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2004177773 EMBASE

TITLE: Characterization of A New **Humanized** Anti-CD20 Monoclonal Antibody, IMMU-106, and Its Use in Combination with the **Humanized** Anti-CD22 Antibody, Epratuzumab, for the Therapy of Non-Hodgkin's Lymphoma.

AUTHOR: Stein R.; Qu Z.; Chen S.; Rosario A.; Shi V.; Hayes M.; Horak I.D.; Hansen H.J.; Goldenberg D.M.

CORPORATE SOURCE: R. Stein, Garden State Cancer Center, 520 Belleville Avenue, Belleville, NJ 07109, United States.
rstein@gscancer.org

SOURCE: Clinical Cancer Research, (15 Apr 2004) 10/8 (2868-2878).
Refs: 49

ISSN: 1078-0432 CODEN: CCREF4

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Purpose: A new **humanized** anti-CD20 monoclonal antibody (MAb), IMMU-106, was evaluated to elucidate its action as an antilymphoma therapeutic, as a single agent, and in combination with the anti-CD22 MAb, epratuzumab. Experimental Design: Antiproliferative effects, apoptotic effects, and the ability of IMMU-106 to mediate complement-mediated cytotoxicity and antibody-dependent cellular cytotoxicity on a panel of non-Hodgkin's lymphoma (NHL) cell lines were compared with the **chimeric** anti-CD20 MAb, rituximab, and evaluated in light of the various levels of antigen expression by the cell lines. In vivo therapy studies were performed in SCID mice bearing disseminated Raji lymphoma. Results: The mechanisms of cytotoxicity of IMMU-106 were found to be similar to rituximab, and include direct apoptosis, antibody-dependent

cellular cytotoxicity, and complement-mediated cytotoxicity. IMMU-106 was also found to be very similar to rituximab in terms of antigen-binding specificity, binding avidity, and dissociation constant. Treatment of Raji-bearing SCID mice with IMMU-106 yielded median survival increases of up to 4.2-fold compared with control mice. Survival in mice treated with IMMU-106 plus epratuzumab was compared with IMMU-106 treatment alone. Although the combined treatment did not improve median survival, an increased proportion of long-term survivors was observed. An enhanced antiproliferative effect was also observed in vitro in SU-DHL-6 cells when IMMU-106 was combined with epratuzumab. These findings are consistent with the up-regulation of CD22 expression observed after pretreatment of NHL cells in vitro with CD20 MAb (IMMU-106). Conclusions: It is expected that in humans IMMU-106 should be at least as effective as rituximab and, due to its **human** framework construction, it may exhibit different pharmacokinetic, toxicity, and therapy profiles. In addition, it may be possible to enhance efficacy by combination therapy comprised of anti-CD20 and other B-cell lineage targeting MAbs, such as epratuzumab. The current results emphasize that in vitro as well as in vivo studies with many of the NHL cell lines were generally predictive of the known activity of anti-CD20 MAbs in NHL patients, as well as the enhanced efficacy of epratuzumab combined with rituximab observed in early clinical trials.

L28 ANSWER 3 OF 30 MEDLINE on STN DUPLICATE 1
 ACCESSION NUMBER: 2004140290 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 14525789
 TITLE: Induction of caspase-dependent programmed cell death in B-cell chronic lymphocytic leukemia by anti-CD22 immunotoxins.
 AUTHOR: Decker Thomas; Oelsner Madlene; Kreitman Robert J; Salvatore Giuliana; Wang Qing-cheng; Pastan Ira; Peschel Christian; Licht Thomas
 CORPORATE SOURCE: III Medizinische Klinik, Klinikum rechts der Isar, Technische Universitat Munchen, Munich, Germany.. t.decker@lrz.tu-muenchen.de
 SOURCE: Blood, (2004 Apr 1) 103 (7) 2718-26.
 Journal code: 7603509. ISSN: 0006-4971.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
 ENTRY MONTH: 200405
 ENTRY DATE: Entered STN: 20040323
 Last Updated on STN: 20040512
 Entered Medline: 20040511
 AB B cells of chronic lymphocytic leukemia (CLL) are long-lived in vivo, possibly because of defects in apoptosis. We investigated BL22, an immunotoxin composed of the Fv portion of an anti-CD22 antibody fused to a 38-kDa **Pseudomonas exotoxin-A** fragment. B cells from 22 patients with CLL were immunomagnetically enriched (96% purity) and were cultured with BL22 or an immunotoxin that does not recognize hematopoietic cells. The antileukemic activity of BL22 was correlated with CD22 expression, as determined by flow cytometry. BL22 induced caspase-9 and caspase-3 activation, poly(adenosine diphosphate [ADP]-ribose)polymerase (PARP) cleavage, DNA fragmentation, and membrane flipping. Cell death was associated with the loss of mitochondrial membrane potential and the down-regulation of Mcl-1 and X-chromosomal inhibitor of apoptosis protein (XIAP). Furthermore, BL22 induced a proapoptotic 18-kDa Bax protein and conformational changes of Bax. Z-VAD.fmk abrogated apoptosis, confirming

that cell death was executed by caspases. Conversely, interleukin-4, a survival factor, inhibited spontaneous death in culture but failed to prevent **immunotoxin**-induced apoptosis. BL22 cytotoxicity was markedly enhanced when combined with anticancer **drugs** including **vincristine**. We also investigated HA22, a newly engineered **immunotoxin**, in which BL22 residues are mutated to improve target binding. HA22 was more active than BL22. In conclusion, these **immunotoxins** induce caspase-mediated apoptosis involving mitochondrial damage. Combination with chemotherapy is expected to improve the efficacy of **immunotoxin** treatment.

L28 ANSWER 4 OF 30 MEDLINE on STN DUPLICATE 2
 ACCESSION NUMBER: 2004088350 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 14977825
 TITLE: The evaluation of recombinant, **chimeric**,
 tetravalent **antihuman CD22**
 antibodies.
 AUTHOR: Meng Ruiqi; Smallshaw Joan E; Pop Laurentiu M; Yen Michael;
 Liu Xiaoyun; Le Lien; Ghetie Maria-Ana; Vitetta Ellen S;
 Ghetie Victor
 CORPORATE SOURCE: The Cancer Immunobiology Center, University of Texas
 Southwestern Medical Center at Dallas, Dallas, Texas
 75390-8576, USA.
 CONTRACT NUMBER: CA64679-07 (NCI)
 SOURCE: Clinical cancer research : an official journal of the
 American Association for Cancer Research, (2004 Feb 15) 10
 (4) 1274-81.
 Journal code: 9502500. ISSN: 1078-0432.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200410
 ENTRY DATE: Entered STN: 20040224
 Last Updated on STN: 20041020
 Entered Medline: 20041019

AB PURPOSE: The purpose of this study was to prepare **chimeric** **antihuman CD22** tetravalent monoclonal antibodies (MAbs) with high functional affinity, long persistence in the circulation, increased antitumor activity, and conserved effector function *in vitro*.
 Experimental Design: We investigated the association/dissociation rates of these tetravalent antibodies using CD22(+) Daudi lymphoma cells. We then tested their ability to interact with Fc receptors on a **human** cell line (U937), to mediate antibody-dependent cellular cytotoxicity with **human** natural killer cells, to bind **human** C1q, to inhibit the *in vitro* growth of CD22 Daudi cells, and to persist in the circulation. RESULTS: The rate of dissociation of the tetravalent MAbs versus the divalent antibody was considerably slower. These tetravalent MAbs inhibited the *in vitro* proliferation of CD22 Daudi cells at a concentration that was at least 100-fold lower than that of the divalent murine antibody. The tetravalent MAbs containing both the CH2 and CH3 domains and a **chimeric** recombinant divalent antibody bound similarly to Fc receptor, C1q, and mediate antibody-dependent cellular cytotoxicity equally well with **human** natural killer cells. The persistence in the circulation of **chimeric** tetravalent MAbs was considerably longer than that of chemical homodimers. CONCLUSIONS: The tetravalent anti-CD22 MAbs with intact Fc regions should make effective therapeutic agents for B-cell tumors.

L28 ANSWER 5 OF 30 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2004490529 IN-PROCESS
 DOCUMENT NUMBER: PubMed ID: 15240561
 TITLE: Cell surface sialic acids do not affect primary CD22 interactions with CD45 and surface IgM nor the rate of constitutive CD22 endocytosis.
 AUTHOR: Zhang Mai; Varki Ajit
 CORPORATE SOURCE: Glycobiology Research and Training Center, Departments of Medicine and Cellular and Molecular Medicine, School of Medicine, University of California, San Diego, La Jolla, CA 92093-0687, USA.
 CONTRACT NUMBER: GM32373 (NIGMS)
 HL57345 (NHLBI)
 SOURCE: Glycobiology, (2004 Nov) 14 (11) 939-49.
 Journal code: 9104124. ISSN: 0959-6658.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
 ENTRY DATE: Entered STN: 20041002
 Last Updated on STN: 20041027

AB CD22/Siglec-2 is a B cell-specific molecule modulating surface IgM (sIgM) signaling via cytosolic tyrosine-based motifs. CD22 recognizes alpha2-6-linked sialic acids (Sias) via an amino-terminal Ig-like domain. This Sia-binding site is typically masked by unknown sialylated ligands on the same cell surface, an interaction required for optimal signaling function. We studied the effect of cell surface Sias on specific interactions of CD22 with other molecules and on its turnover via endocytosis. A novel approach for simultaneous biotinylation and cross-linking showed that CD22 associates with CD45 and sIgM at much higher levels than reported in prior studies, possibly involving cell surface multimers of CD22. Sia removal or mutation of a CD22 arginine residue required for Sia recognition did not affect these associations even in human:mouse heterologous systems, indicating that they are primarily determined by evolutionarily conserved protein-protein interactions. Thus masking of the Sia-binding site of CD22 involves many cell surface sialoglycoproteins, without requiring specific ligand(s) and/or is mediated by secondary interactions with Sias on CD45 and sIgM. Abrogating Sia interactions also does not affect constitutive CD22 endocytosis. Sia removal does enhance the much faster rate of **anti-CD22 antibody**-triggered endocytosis, as well as killing by an anti-CD22 **immunotoxin**. In contrast to the unstimulated state, sIgM cross-linking inhibits both antibody-induced endocytosis and **immunotoxin** killing. Thus the signal-modulating activity of CD22 Sia recognition cannot be explained by mediation of primary interactions with specific molecules, nor by effects on constitutive endocytosis. The effects on antibody-mediated endocytosis could be of relevance to **immunotoxin** treatment of lymphomas.

L28 ANSWER 6 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN

ACCESSION NUMBER: 2003388514 EMBASE
 TITLE: Epratuzumab, a **humanized** monoclonal antibody targeting CD22: Characterization of *in vitro* properties.
 AUTHOR: Carnahan J.; Wang P.; Kendall R.; Chen C.; Hu S.; Boone T.; Juan T.; Talvenheimo J.; Montestruque S.; Sun J.; Elliott G.; Thomas J.; Ferbas J.; Kern B.; Briddell R.; Leonard J.P.; Cesano A.
 CORPORATE SOURCE: J. Carnahan, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, United States. jcarnaha@amgen.com
 SOURCE: Clinical Cancer Research, (1 Oct 2003) 9/10 II

(3982s-3990s).

Refs: 32

ISSN: 1078-0432 CODEN: CCREF4

COUNTRY:

United States

DOCUMENT TYPE:

Journal; Conference Article

FILE SEGMENT:

016 Cancer

026 Immunology, Serology and Transplantation

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Purpose: Epratuzumab is a novel **humanized antihuman**

CD22 IgG1 antibody that has recently shown promising clinical activity, both as a single agent and in combination with rituximab, in patients with non-Hodgkin's lymphomas (NHL). In an attempt to better understand the mode of action of epratuzumab, the antibody was tested in vitro in a variety of cell-based assays similar to those used to evaluate the biological

activity of other therapeutic monoclonal antibodies, including rituximab. In this report, we present epratuzumab activities as they relate to binding, signaling, and internalization of the receptor CD22. Methods:

Chinese hamster ovary-expressed CD22 extracellular domain was used to measure epratuzumab affinity on Biacore. CD22 receptor density and internalization rate were measured indirectly using a monovalently labeled, noncompeting (with epratuzumab) **anti-CD22**

antibody on Burkitt lymphoma cell lines, primary B cells derived from fresh tonsils, and B cells separated from peripheral blood samples obtained from patients with chronic lymphocytic leukemia or healthy volunteers. Epratuzumab-induced CD22 phosphorylation was measured by immunoprecipitation/Western blot and compared with that induced by anti-IgM stimulation. Results: Epratuzumab binds to CD22-extracellular domain, with an affinity of $K(D) = 0.7 \text{ nM}$. Binding of epratuzumab to B cell lines, or primary B cells from healthy individuals and patients with NHL, results in rapid internalization of the CD22/antibody complex.

Internalization appears to be faster at early time points in cell lines than in primary B cells and NHL patient-derived B cells, but the maximum internalization reached is comparable for all B cell populations after several hours of treatment and appears to reach saturation at antibody concentrations of 1-5 $\mu\text{g/ml}$. Finally, epratuzumab binding results in modest but significant CD22 phosphorylation. Conclusions: Epratuzumab represents an excellent anti-CD22 ligating agent, highly efficacious in inducing CD22 internalization, and can induce phosphorylation. Although we cannot unequivocally demonstrate here that epratuzumab-induced

internalization and signaling of CD22 directly contribute to its therapeutic efficacy, these properties are the fundamental characteristics of the target CD22 and its interaction with epratuzumab. Similar results were observed when epratuzumab was tested in vitro on Burkitt B cell lines as well as on primary normal B cells and neoplastic B cells separated from fresh peripheral blood samples from patients with chronic lymphocytic leukemia.

L28 ANSWER 7 OF 30 MEDLINE on STN

ACCESSION NUMBER: 2003379686 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12837807

TITLE: Phase I/II trial of epratuzumab (**humanized anti-CD22 antibody**) in indolent non-Hodgkin's lymphoma.

COMMENT: Comment in: J Clin Oncol. 2003 Aug 15;21(16):3011-2. PubMed ID: 12837808

AUTHOR: Leonard John P; Coleman Morton; Ketas Jamie C; Chadburn Amy; Ely Scott; Furman Richard R; Wegener William A; Hansen Hans J; Ziccardi Heather; Eschenberg Michael; Gayko Urte;

CORPORATE SOURCE: Cesano Alessandra; Goldenberg David M
 Center for Lymphoma and Myeloma, Division of Hematology and
 Oncology, Weill Medical College of Cornell University and
 New York Presbyterian Hospital, 520 East 70th Street, New
 York, NY 10021, USA.. jpleonar@med.cornell.edu

CONTRACT NUMBER: RR 16814-02 (NCRR)

SOURCE: Journal of clinical oncology : official journal of the
 American Society of Clinical Oncology, (2003 Aug 15) 21
 (16) 3051-9.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)
 (CLINICAL TRIAL, PHASE I)
 (CLINICAL TRIAL, PHASE II)
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200309

ENTRY DATE: Entered STN: 20030814
 Last Updated on STN: 20030916
 Entered Medline: 20030915

AB PURPOSE: This single-center, dose-escalation study examines the safety, efficacy, and pharmacokinetics of epratuzumab (anti-CD22 **humanized** monoclonal antibody) in patients with recurrent indolent non-Hodgkin's lymphoma (NHL). PATIENTS AND METHODS: Patients had indolent NHL and recurrent disease after at least one chemotherapy regimen. Epratuzumab was administered intravenously at 120 to 1,000 mg/m² over 30 to 60 minutes weekly for four treatments. RESULTS: Fifty-five patients received epratuzumab and were assessable for safety; 51 patients were assessable for response. Patients were heavily pretreated (50% had at least four prior regimens) and 49% had bulky disease (> or = 5 cm). Epratuzumab was well tolerated, with no dose-limiting toxicity. Circulating B cells transiently decreased without significant effects on T cells or immunoglobulin levels. More than 95% of infusions were completed in approximately 1 hour. Mean serum half-life was 23 days. Across all dose levels and histologies, nine patients (18%; 95% confidence interval, 8% to 31%) achieved objective response, including three complete responses (CRs). All responses were in patients with follicular NHL: 24% of these patients responded, including 43% in the 360 mg/m² dose group and 27% in the 480 mg/m² dose group. No responses were observed in other indolent histologies. Median duration of objective response was 79.3 weeks (range, 11.1 to 143.3 weeks), with median time to progression for responders of 86.6 weeks by Kaplan-Meier estimate. CONCLUSION: Epratuzumab was well tolerated at up to 1,000 mg/m²/wk (for 4 weeks) and had clinical activity. One third of responding patients achieved CR. A 43% objective response rate in follicular NHL patients treated at 360 mg/m²/wk indicates that this dose should be explored in additional studies.

L28 ANSWER 8 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2004:152053 BIOSIS

DOCUMENT NUMBER: PREV200400147703

TITLE: Anti-tumor efficacy of CMC-544, a CD22-targeted immunoconjugate of calicheamicin, in a systemically disseminated B-cell lymphoma.

AUTHOR(S): DiJoseph, John F. [Reprint Author]; Goad, Mary E.; Dougher, Maureen M. [Reprint Author]; Boghaert, Erwin R. [Reprint Author]; Damle, Nitin K. [Reprint Author]

CORPORATE SOURCE: Oncology Discovery, Wyeth Research, Pearl River, NY, USA
 SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 645a.

print.

Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003.
American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 17 Mar 2004

Last Updated on STN: 17 Mar 2004

AB The systemically disseminated B-cell lymphoma (BCL) model in SCID mice mimics the clinical course of BCL in **humans**. In this model, malignant **human** B cells are injected IV in SCID mice to facilitate their dissemination throughout the body (diseased mice) resulting in hind-limb paralysis and death from BCL infiltration into the central nervous system. CMC-544 is an immunoconjugate in which N-acetyl gamma calicheamicin dimethyl hydrazide (CalichDMH) is covalently linked via an acid-labile AcBut linker to a **humanized IgG4 anti-CD22 antibody**, G5/44, developed at Celltech. CMC-544 was shown to exert potent cytotoxicity against CD22+ BCL. This study evaluated anti-tumor activity of CMC-544 against systemically disseminated CD20+ CD22+ CD33- Ramos BCL in SCID mice. CMA-676, a CD33-targeted immunoconjugate of CalichDMH, was used as an isotype-matched, negative control. Effects of unconjugated G5/44 and rituximab, a CD20-targeted chimeric IgG1 antibody were evaluated in the same model. All treatments were administered IP as 3 doses, given 4 days apart (Q4DX3). All vehicle-treated diseased mice developed hind limb paralysis with an average survival time of 32 days. CMC-544 at doses of 40 and 80 mug of CalichDMH equivalents/kg was strongly protective with 90% of diseased mice surviving for >120 days (final time point in this evaluation) and were considered, cured. CMC-544, at the highest dose of 160 mug/kg, prevented hind-limb paralysis in all diseased mice but their survival was shortened (average survival time of 66 days). This dose of CMC-544 is higher than its maximum nonlethal dose in SCID mice. Neither the unconjugated G5/44 (20 mg/kg Q4DX3) nor the isotype-matched control conjugate, CMA-676 (40 and 160 mug/kg), conferred any protection against the systemic disease with 90% of treated mice being paralyzed or dead before day 40. The lack of anti-tumor activity of unconjugated G5/44 is consistent with its IgG4 isotype that is unable to mediate antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. Rituximab (20 mg/kg Q4DX3) produced complete protection against the systemic BCL (survival time of >120 days) only when administered early (day 3) during the disease progression. Delaying rituximab treatment until day 9 resulted in significant loss of its anti-BCL effect (average survival time of 40 days). The increased tumor burden at day 9 may have limited the ability of rituximab to mediate its anti-tumor activity. Protection conferred by CMC-544 against systemic BCL was apparent regardless of whether the conjugate was administered early (day 3) or late (day 9) during the disease progression. Histopathological analysis of selected organs from the vehicle-treated diseased mice with hind limb paralysis demonstrated BCL infiltration in brain (100% of mice), spinal cord (43% of mice), bone marrow (100% of mice) and kidney (71% of mice). In contrast, no BCL infiltration was detected in tissues from CMC-544-treated diseased mice when analyzed on day 32. These results demonstrate that CMC-544 can eliminate BCL disseminated throughout the body resulting in prolonged survival of diseased mice and support further exploration of CMC-544 as a therapeutic agent for B lymphoid malignancies. CMC-544 is currently being evaluated as a targeted chemotherapeutic agent in patients with non-Hodgkin's lymphoma in a multicenter phase I trial.

L28 ANSWER 9 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2004:150253 BIOSIS
DOCUMENT NUMBER: PREV200400146923
TITLE: Induction of caspase-dependent programmed cell death in
B-CLL cells by recombinant anti-CD22 immunotoxins

AUTHOR(S): Decker, Thomas [Reprint Author]; Oelsner, Madlene [Reprint
Author]; Kreitman, Robert J.; Salvatore, Giuliana; Wang,
Qing-Cheng; Pastan, Ira; Peschel, Christian [Reprint
Author]; Licht, Thomas [Reprint Author]

CORPORATE SOURCE: 3rd Department of Internal Medicine (Hematology/Oncology),
Klinikum Rechts der Isar, Technical University, Munich,
Germany

SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 439a.
print.
Meeting Info.: 45th Annual Meeting of the American Society
of Hematology. San Diego, CA, USA. December 06-09, 2003.
American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB Induction of apoptosis is thought to be defective in B-cell chronic
lymphocytic leukemia (B-CLL) cells in peripheral blood. We investigated
the activity of BL22, a recombinant **immunotoxin** composed of the
Fv portion of an **anti-CD22 antibody** fused to
a 38kDa fragment of **Pseudomonas exotoxin A**. B-cells
from 22 CLL patients were immunomagnetically enriched to >96% purity,
and cultured in the presence of BL22 or an **immunotoxin** that does
not recognize hematopoietic cells. The antileukemic activity of BL22 was
closely correlated with the level of CD22 expression as determined by flow
cytometry. BL22 induced cell death after a 2h-exposure, which was further
increased by continuous incubation for 72h. The **immunotoxin**
induced caspase-9 and caspase-3 activation, poly(ADP-ribose)polymerase
(PARP) cleavage, DNA fragmentation as assessed with a TUNEL assay, and
membrane flipping as assessed with Annexin V staining. Cell death was
associated with loss of mitochondrial membrane potential and
down-regulation of antiapoptotic proteins, Mcl-1 and XIAP while Bcl-2
levels remained unchanged. Time course experiments revealed that damage
to mitochondria preceded caspase-3 activation. Furthermore, BL22 induced
conformational changes of Bax and proapoptotic 18 kDa Bax protein. The
caspase inhibitor Z-VAD fmk almost completely abrogated caspase-3
activation, DNA strand breaks and membrane flipping, confirming that cell
death was executed by caspase activation. Conversely, interleukin-4, an
antiapoptotic survival factor, inhibited spontaneous cell death in
culture, but failed to prevent from **immunotoxin**-induced
apoptosis. The cytotoxicity of BL22 was markedly enhanced when combined
with anticancer drugs including vincristine or
doxorubicin. We also investigated HA22, a newly engineered
immunotoxin, in which residues of BL22 are mutated to improve
target binding. HA22 was much more active against B-CLL cells than BL22.
In conclusion, these **immunotoxins** induce caspase-mediated
apoptosis involving mitochondrial damage. Combination with anticancer
chemotherapy is expected to improve the efficacy of **immunotoxin**
treatment.

L28 ANSWER 10 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2004:150107 BIOSIS

DOCUMENT NUMBER: PREV200400146800

TITLE: Outcome and absorbed dose following 90-Yttrium-Epratuzumab in B-cell lymphoma, using a dose-fractionation schedule.

AUTHOR(S): Linden, Ola [Reprint Author]; Hindorf, Cecilia; Cavallin-Stahl, Eva [Reprint Author]; Ohlsson, Tomas; Strand, Sven-Erik; Wegener, William A.; Ziccardi, Heather; Goldenberg, David M.; Tennvall, Jan [Reprint Author]

CORPORATE SOURCE: Department of Oncology, Lund University Hospital, Lund, Sweden

SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 407a.
print.

Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003.
American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 17 Mar 2004

Last Updated on STN: 17 Mar 2004

AB Fractionated RIT may improve therapeutic outcome by decreasing heterogeneity in absorbed dose to tumor and by increasing the therapeutic window. The **humanized anti-CD22 antibody**, Epratuzumab (Immunomedics, Inc., Morris Plains, NJ) can be given repeatedly with no or minimal risk for neutralising Ab (HAHA), making fractionated treatment with 90Y labeled Epratuzumab feasible. Patients with B-cell lymphoma relapsing or resistant to standard chemotherapy were treated in cohorts of 3-6 pts with increasing number (2-4) of weekly infusions of 90Y-Epratuzumab. Twenty-three patients with various subtypes of B-cell lymphoma; (transformed n=5; diffuse large B-cell n=6; follicular grade II n=6; follicular grade III n=1 mantle cell n=3; MALT n=1; B-CLL n=1) received either 5mCi/m²/infusion (group A), or 2.5mCi/m²/infusion (group B) if they had a history of prior high-dose chemotherapy with stem cell rescue. The first infusion for all patients also included 4 mCi of 111Indium for a scintigraphic verification of tumor targeting. A total amount of 1.5 mg/kg Epratuzumab was administered with each infusion. The treatment could be repeated once after 3 months, provided there was neither severe toxicity nor progression of disease. Of 23 patients, 16 in group A and 6 in group B are evaluable for response. Response in group A was 62% OR and 25% CR/CRu. Response was seen in indolent as well as in aggressive lymphomas with a duration of CR/CRu from 14 to 41 months. Toxicity was mainly hematological. In group B no patient suffered grade ≥3. In group A, grade 3 toxicity was seen in 0/3, 3/7 and in 2/4 evaluable patients at the 2, 3 and 4 infusion level, respectively. Grade 4 toxicity was only observed in 2 patients at the four infusion level, recently treated with high-dose cytosar. The median absorbed dose, from first infusion only, to tumor in 12 patients in group A, was 3.8 Gy, range 0.9 to 9.6 Gy. The median absorbed dose to tumor was 11.5 mGy/MBq, range 30.3 to 2.2 mGy/MBq. In 2/2 patients, where the absorbed dose to tumor could be estimated at retreatment, the dose at retreatment was doubled compared with the first infusion. Median absorbed dose from the first infusion, in 16 patients in group A, was 1.6 Gy to the kidneys, 1.3 Gy to the liver, 2.1 Gy to the lungs, 0.4 Gy to the bone marrow, 2.4 Gy to the spleen and 0.2 Gy to the whole body. The median absorbed dose to tumor was 11.5 mGy/MBq, range 2.2 to 30.3 mGy/MBq. RIT

of B-cell lymphoma employing repeated weekly infusions with radiolabeled hLL2 (5mCi 90Y/m2) can result in durable objective remission in patients with various subtypes of lymphoma, which have failed prior chemotherapy. Three weekly infusions 5mCi/m2 can safely be administered with only minor hematological toxicity. Absorbed dose to tumor varies significantly inter- and intraindividually.

L28 ANSWER 11 OF 30 MEDLINE on STN DUPLICATE 4
 ACCESSION NUMBER: 2003200170 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12720147
 TITLE: CD22 as a target of passive immunotherapy.
 AUTHOR: Cesano Alessandra; Gayko Urte
 CORPORATE SOURCE: Amgen Inc, Thousand Oaks, CA 91320, USA.
 SOURCE: Seminars in oncology, (2003 Apr) 30 (2) 253-7. Ref: 40
 Journal code: 0420432. ISSN: 0093-7754.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200306
 ENTRY DATE: Entered STN: 20030430
 Last Updated on STN: 20030603
 Entered Medline: 20030602

AB CD22 is a 135-kd B-cell restricted sialoglycoprotein present in the cytoplasm of virtually all B-lineage cells but expressed on the B-cell surface only at mature stages of differentiation. In **humans**, the vast majority of IgM(+) IgD(+) B cells express cell-surface CD22, while in lymphoid tissues CD22 expression is high in follicular mantle and marginal zone B cells and weak in germinal center B cells. In B-cell malignancies, CD22 expression ranges from 60% to 80% depending on the histological type and on the assays used. The function of the CD22 molecule is uncertain, although recent studies have suggested roles for the molecule both as a component of the B-cell activation complex and as an adhesion molecule. CD22-deficient mice have a reduced number of mature B cells in the bone marrow and circulation; the B cells have a shorter lifespan and enhanced apoptosis, thus indicating a key role of this antigen in B-cell development/survival. After binding with its natural ligand(s) or antibodies, CD22 is rapidly internalized; this provides a potent costimulatory signal in primary B-cell and proapoptotic signals in neoplastic B cells. Preclinically CD22 has been shown to be an effective target for immunotherapy of B-cell malignancies using either "naked" or **toxin**-labeled or radiolabeled monoclonal antibodies. Clinical trials in patients with non-Hodgkin's lymphoma (NHL) (both indolent and aggressive disease) are now ongoing with a **humanized** naked **anti-CD22 antibody** (epratuzumab, Amgen Inc, thousand Oaks, CA and Immunomedics Inc, Morris Plains, NJ) used as single agent or in combination with other monoclonal antibodies (ie, rituximab) and/or chemotherapy. Preliminary data from these studies showed these approaches to be effective and well-tolerated.
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L28 ANSWER 12 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
 ACCESSION NUMBER: 2003:392715 BIOSIS
 DOCUMENT NUMBER: PREV200300392715
 TITLE: Predictive value of FDG-PET for response to radiolabeled monoclonal antibody treatment for NonHodgkins lymphoma.
 AUTHOR(S): Rebenstock, A. [Reprint Author]; Dadparvar, S.; Johnson,

CORPORATE SOURCE: G.; Reich, P. E.; Zhuang, H. M.; Newberg, A. B.; Schuster, S. J.; Alavi, A.
 Radiology, University of Pennsylvania, Philadelphia, PA,
 USA

SOURCE: Journal of Nuclear Medicine, (May 2003) Vol. 44, No. 5
 Supplement, pp. 188P. print.
 Meeting Info.: 50th Annual Meeting of the Society of
 Nuclear Medicine. New Orleans, LA, USA. June 21-25, 2003.
 Society of Nuclear Medicine.
 ISSN: 0161-5505 (ISSN print).

DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 27 Aug 2003
 Last Updated on STN: 27 Aug 2003

L28 ANSWER 13 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN

ACCESSION NUMBER: 2003222111 EMBASE
 TITLE: Current treatment strategies for patients with hairy cell leukemia.
 AUTHOR: Tallman M.S.
 CORPORATE SOURCE: Dr. M.S. Tallman, NW. Univ. Feinberg Sch. of Medicine,
 Robert H. Lurie Compreh. Cancer Ctr., 676 N. St. Clair
 Street, Chicago, IL 60611, United States
 SOURCE: Reviews in Clinical and Experimental Hematology, (2002) 6/4
 (389-400).
 Refs: 84
 ISSN: 1127-0020 CODEN: RCEHFB
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 016 Cancer
 025 Hematology
 037 Drug Literature Index
 038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Hairy cell leukemia is uncommon, but recent developments in treatment have improved the outcome. Splenectomy was the preferred treatment for many years until the efficacy of interferon was clearly demonstrated. Currently, the purine analogs have emerged as the treatments of choice. 2-Chlorodeoxyadenosine (2-CdA) is resistant to the action of adenosine deaminase. Since this agent generally is administered as a single 7-day course with a paucity of toxicities, many investigators have suggested it is the preferable agent. However, the outcome associated with 2-CdA has never been compared to 2-deoxycoformycin in a prospective randomized trial. Therefore, it is not known whether one or the other agent is associated with improved long-term outcome. The new immunotoxin, BL22, which is a fusion of an anti-CD22 antibody linked to a portion of the *Pseudomonas exotoxin* A, has proved to be very effective for patients who have failed or are refractory to the purine analogs. The role of this agent as initial therapy for newly diagnosed patients has not been explored.

L28 ANSWER 14 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2002:452309 BIOSIS
 DOCUMENT NUMBER: PREV200200452309
 TITLE: Use of galactosylated-streptavidin as a clearing agent with

AUTHOR(S): Govindan, Serengulam V.; Griffiths, Gary L.; Michel, Rosana B.; Andrews, Philip M.; Goldenberg, David M.; Mattes, M. Jules [Reprint author]

CORPORATE SOURCE: Center for Molecular Medicine and Immunology, 520 Belleville Avenue, Belleville, NJ, 07109, USA
mjmattes.gscancer@worldnet.att.net

SOURCE: Cancer Biotherapy and Radiopharmaceuticals, (2002) Vol. 17, No. 3, pp. 307-316. print.
ISSN: 1084-9785.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 21 Aug 2002
Last Updated on STN: 21 Aug 2002

AB Optimal tumor imaging using radiolabeled antibodies (Abs) depends on obtaining the highest possible tumor/non-tumor localization ratios. To increase this ratio, in a mouse xenograft model system, we induced rapid blood clearance of the Ab after extensive penetration of a solid tumor, at 24 hr after Ab injection. By using galactosylated streptavidin (gal-SA) as a clearing agent for biotinylated Abs, and by using an ¹¹¹In-DTPA (diethylenetriaminepentaacetic acid) label, clearance was directed to hepatocytes (as opposed to Kupffer cells), and the radiolabel was excreted by the hepatocytes into bile, thereby reducing accumulation in the liver. In this study, we directly compared this approach with the use of ^{99m}Tc-F(ab)₂ fragments, using the same Ab to carcinoembryonic antigen (CEA), with a colon carcinoma xenograft. The gal-SA clearance method produced substantially higher tumor/non-tumor localization ratios for all tissues except the liver, and even for the liver the disadvantage of the gal-SA clearance method was small. We also tested the gal-SA clearance method with a xenograft model of **human** B-cell lymphoma, using anti-CD22. High tumor/non-tumor ratios were obtained, as previously described with carcinomas of the lung and colon. Therefore, this approach appears to be a generally applicable strategy to obtain relatively high tumor/non-tumor ratios.

L28 ANSWER 15 OF 30 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2002438255 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12195750

TITLE: ¹³¹I-labelled anti-CD22 MAb (LL2) in patients with B-cell lymphomas failing chemotherapy. Treatment outcome, haematological toxicity and bone marrow absorbed dose estimates.

AUTHOR: Linden Ola; Tennvall Jan; Hindorf Cecilia; Cavallin-Stahl Eva; Lindner Karl-Johan; Ohlsson Tomas; Wingardh Karin; Strand Sven-Erik

CORPORATE SOURCE: Department of Oncology, Lund University Hospital, SE-221 85 Lund, Sweden.. ola.linden@onk.lu.se

SOURCE: Acta oncologica (Stockholm, Sweden), (2002) 41 (3) 297-303. Journal code: 8709065. ISSN: 0284-186X.

PUB. COUNTRY: Norway

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200209

ENTRY DATE: Entered STN: 20020829
Last Updated on STN: 20020911
Entered Medline: 20020910

AB The experience with radioimmunotherapy in B-cell lymphomas using the rapidly internalizing antibody, anti-CD22 (LL2), is limited. In this

study we investigated the efficacy and toxicity of ^{131}I -labelled-LL2 for radioimmunotherapy in patients with B-cell lymphomas that failed one or two cytostatic regimens. Eleven patients were treated with one or repeated cycles of ^{131}I -anti-CD22 antibody, 1330 MBq/m^2 (36 mCi/m^2). Six of the 11 treated patients demonstrated an objective response, three of them with complete remission. All follicular (3 patients) and transformed lymphomas (2 patients) responded compared to one of four diffuse large B-cell lymphomas. Two out of six responders exhibited event-free survival (EFS), which was comparable with or longer than the EFS following primary anthracycline-containing chemotherapy. Non-haematological toxicity was mild. Haematological toxicity was associated with pretreatment clinical characteristics but not with estimated absorbed bone marrow doses. Objective remission following treatment with ^{131}I -anti-CD22 can be achieved in patients with various subtypes of B-cell lymphomas, failing standard chemotherapy. Follicular or transformed lymphomas seem particularly responsive. Haematological toxicity seems to be dependent on the functional status of the bone marrow before radioimmunotherapy.

L28 ANSWER 16 OF 30 MEDLINE on STN DUPLICATE 6
 ACCESSION NUMBER: 2002151689 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11883697
 TITLE: Technology evaluation: BL22, NCI.
 AUTHOR: Barth Stefan
 CORPORATE SOURCE: Institute of Biology, Aachen, Germany..
 bARTH@molbiotech.rwth-aachen.de

SOURCE: Current opinion in molecular therapeutics, (2002 Feb) 4 (1)
 72-5. Ref: 13
 Journal code: 100891485. ISSN: 1464-8431.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200209
 ENTRY DATE: Entered STN: 20020311
 Last Updated on STN: 20020917
 Entered Medline: 20020916

AB BL22 (RFB4(dsFv)-PE38) is a recombinant *Pseudomonas* exotoxin-based immunotoxin under development by the National Cancer Institute for the treatment of B-cell malignancies. It is composed of the disulfide-stabilized Fv portion of the anti-CD22 antibody RFB4 genetically fused to a truncated form of *Pseudomonas* exotoxin A. It has entered phase I trials for the treatment of B-cell lymphoma.

L28 ANSWER 17 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
 ACCESSION NUMBER: 2003:356645 BIOSIS
 DOCUMENT NUMBER: PREV200300356645
 TITLE: CMC-544, an Anti-CD22 Antibody -Targeted Calicheamicin Therapeutic for the Treatment of B Lymphoid Malignancies.
 AUTHOR(S): DiJoseph, John [Reprint Author]; Armellino, Doug; Khandke, Kiran; Boghaert, Erwin; Dougher, Maureen; Sridharan, Latha; Kunz, Art; Moran, Justin; Hamann, Philip; Frost, Philip; Damle, Nitin
 CORPORATE SOURCE: Oncology Discovery, Wyeth Research, Pearl River, NY, USA
 SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract

No. 599. print.

Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 6 Aug 2003

Last Updated on STN: 6 Aug 2003

AB Antibody-targeted chemotherapy takes advantage of the preferential delivery of a cytotoxic agent to the tumor thereby sparing the rest of the body undue exposure to the same cytotoxic agent. This strategy has been clinically validated in form of MylotargTM, a CD33-targeted immunoconjugate of calicheamicin (gemtuzumab ozogamicin), which represents the first US FDA approved antibody-targeted chemotherapeutic. Calicheamicin is a potent cytotoxic agent that binds to the minor groove of DNA in a sequence specific manner ultimately leading to double stranded DNA breaks and cell death. Employing the same innovative AcBut linker technology as in MylotargTM, a **humanized** IgG4 anti-CD22 monoclonal antibody (G544) was conjugated to calicheamicin to create CMC-544. CMC-544 is intended to treat CD22+ B-cell malignancies, including non-Hodgkin's lymphoma. CMC-544 binds the CD22 antigen with similar affinity as the unconjugated antibody G544 ($KD = 120 \text{ pM}$). CMC-544 was cytotoxic against a series of CD22+ B cell lines (IC_{50} s 10-500 pM calicheamicin equivalents), being at least 20-fold more potent than calicheamicin conjugated to an isotype matched, nonbinding control antibody. Unconjugated G544 antibody had no effect on the growth of the B cell lines. The circulating half-life ($t_{1/2}$) of CMC-544 measured in nude mice was 35 hr after a single ip dose of the conjugate. The exposure levels (AUC) of CMC-544 were 36% lower in B lymphoma tumor-bearing mice than those without tumors indicative of the ability of CMC-544 to target and be absorbed by the tumor. When evaluated in established subcutaneous Ramos and RL B lymphoma xenografts in nude mice, CMC-544 significantly inhibited tumor growth when administered ip on days 1, 5, 9 post-tumor staging (q4dx3). This dosing regimen was followed throughout these studies. The minimum efficacious dose of CMC-544 was 20 mug calicheamicin equivalents/kg, while the ED90 was 52 mug calicheamicin equivalents/kg. At higher doses, complete regression of B-cell lymphomas was achieved and maintained for >100 days leading to cures. Neither unconjugated calicheamicin, unconjugated G544, nor an irrelevant antibody conjugated to calicheamicin had any effect on these xenografts. The LD10 of CMC-544 in nude mice was determined to be 256 mug calicheamicin equivalents/kg, giving a therapeutic index (LD10/ED90) of 5. CMC-544, at 160 mug calicheamicin/kg, caused almost complete regression of large B-cell lymphomas (initial tumor mass of 1.5 to 2 g) in both Ramos and RL xenografts. In a disseminated Ramos B lymphoma model in scid mice, CMC-544 significantly prolonged survival of the mice. These results suggest that the CMC-544 effectively targets CD22+ B lymphomas and causes their regression at doses significantly lower than its maximum tolerated dose. This preclinical demonstration of anti-tumor efficacy of CMC-544 in both subcutaneous and disseminated B-cell lymphoma models strongly supports the clinical use of CMC-544 in the treatment of **human** B-cell lymphoid malignancies.

L28 ANSWER 18 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2003:335958 BIOSIS

DOCUMENT NUMBER: PREV200300335958

TITLE: Differential Expression of CD22 in Indolent and Aggressive Non-Hodgkin's Lymphoma (NHL): Implications for Targeted Immunotherapy.

AUTHOR(S): Cesano, Alessandra [Reprint Author]; Gayko, Urte [Reprint Author]; Brannan, Carol [Reprint Author]; Kapushoc, Heather [Reprint Author]; Fields, Scott Z. [Reprint Author]; Perkins, Sherri L. [Reprint Author]

CORPORATE SOURCE: Amgen Inc., Thousand Oaks, CA, USA

SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 1358. print.

Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002.

American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)

Conference; (Meeting Poster)

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ENTRY DATE: Entered STN: 23 Jul 2003

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AB Expression of the CD22 molecule by neoplastic B-cells provides a promising target for therapy of B-cell malignancies. CD22 is a 135-kD B-cell restricted sialoglycoprotein present in the cytoplasm of virtually all cells of B lineage although it is expressed on the cell surface (in detectable levels) only at mature stages of B-cell differentiation. Because CD22 is known to be internalized after interaction with its natural ligands and to traffic from the Golgi apparatus to cell membranes, the localization of CD22 within cells may reflect different cellular status (ie, receptor-ligand internalization; newly synthesized molecules to be inserted into the membrane). Understanding the differential expression and cellular localization of CD22 in different B-cell malignancies may be important in order to optimize the development of antibody-mediated anti-CD22 targeted therapy. Methods: 75 formalin-fixed, paraffin-embedded (FFPE) tumor samples from patients with low-grade NHL (n=63) and diffuse large-cell lymphoma (DLCL) (n=17) enrolled in ongoing clinical studies with epratuzumab (Amgen Inc, CA and Immunomedics Inc, NJ) were evaluated immunohistochemically (IHC) for CD22 expression and cellular localization using a commercially available anti-CD22 antibody (Novocastra NCL-22-2, clone FPC-1). All samples had appropriate internal control (ie, reactive B-cell staining). CD22 expression was scored by an independent pathologist; membrane and cytoplasmic staining for CD22 was scored separately on a four-bracket scale and the intensity was graded based on a visual assessment from low to high. Results: CD22 expression was detected in 98.4% (62 out of 63) low-grade NHL samples and in 82% (14 out of 17) DLCL samples. In general, the CD22 membrane staining was low based on the expression scale and the intensity of the staining. The most common CD22 phenotype consisted of positivity in both the membrane and the cytoplasm while a small subset (12.7% in the low-grade NHL and 6% in the DLCL samples) demonstrated positivity only in the cytoplasm. CD22 expression was more heterogeneous in the low-grade NHL samples compared to DLCL samples: 47% of DLCL samples had CD22 positivity with high intensity while only 17.5% of tumors from patients with low-grade NHL presented this phenotype. Conclusions: in summary, the above data suggest that a) CD22 expression can be successfully measured by IHC on FFPE sections from historically collected NHL tumor samples; b) CD22 positivity appears to be mostly related to cytoplasm staining; c) there might be a differential expression of CD22 in indolent versus aggressive NHL. To our knowledge, the clinical significance of cellular localization (membrane versus cytoplasmic) of CD22 in different histologic types of NHL and its importance for NHL

treatment with targeted immunotherapy has not been addressed previously: investigation into the staining pattern of NHL and response to therapy with epratuzumab are in progress.

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ACCESSION NUMBER: 2003:336959 BIOSIS
DOCUMENT NUMBER: PREV200300336959

TITLE: The Effect of Epratuzumab on Peripheral Blood B-Cell Levels in Normal, Male Cynomolgus Monkeys.

AUTHOR(S): Briddell, Robert [Reprint Author]; Kern, Brent [Reprint Author]; Stoney, Gregory [Reprint Author]; Sutherland, Weston [Reprint Author]; Perotti, Beatrice [Reprint Author]; Radinsky, Robert [Reprint Author]; Molineux, Graham [Reprint Author]; Cesano, Alessandra [Reprint Author]

CORPORATE SOURCE: Hematology, Amgen Inc., Thousand Oaks, CA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 2262. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002.
American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

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Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jul 2003
Last Updated on STN: 23 Jul 2003

AB Epratuzumab (E-mab; hLL2, Immunomedics, Inc.), a **humanized** monoclonal antibody directed against CD22, a cell surface glycoprotein expressed by normal and malignant B-cells, is under clinical development for the treatment of B-cell non-Hodgkin's lymphoma. Since normal B-cells express CD22, in this study we have investigated the effect of escalating doses of E-mab on peripheral blood B-cell levels of hematologically normal, male Cynomolgus monkeys. Fifteen male Cynomolgus monkeys were arranged into 5 treatment cohorts of 3 animals each, and each animal was treated weekly for 4 weeks with a 2-hour intravenous injection with either saline, Rituxan(R) (375 mg/m²) or escalating doses of E-mab (300, 900 or 2,000 mg/m²). Complete blood counts from each animal, as well as E-mab pharmacokinetics, were evaluated twice weekly for 16 weeks. B-cell levels were evaluated using flow cytometry with a phycoerythrin-conjugated murine anti-**human** CD22 antibody (Caltag Laboratories) for the Rituxan(R) cohort or a phycoerythrin-conjugated murine anti-**human** CD20 antibody (BD Biosciences) for the 3 E-mab cohorts. Both antibodies were used to assess the saline cohort. Results showed that the animals treated with Rituxan(R) had no detectable circulating B-cells after the first injection, while animals treated with E-mab at all doses showed a partial decrease in circulating B-cells of approximately 70% compared with baseline levels after the first injection. There was no statistically significant difference in B-cell levels between the 3 E-mab cohorts. Although the percentage reduction in B-cells in the 3 E-mab cohorts was similar, the serum exposure of E-mab increased with increasing doses. Following the first injection, the mean Cmax achieved by the 300, 900 and 2,000 mg/m² cohorts were 594, 1,500 and 3,530 mug/mL respectively. E-mab serum concentrations obtained after the fourth injection indicated a half-life of 4.4 to 6.3 days. Recovery of B-cell levels in E-mab-treated animals occurred 7 weeks after the fourth injection, while only a partial recovery of B-cell levels in Rituxan(R)-treated animals was observed at the end of the 16-week study. There was no statistically significant

effect on B-cell levels in animals in the saline cohort at any time during the study, and there was no statistically significant effect on any of the other measured hematological compartments during the course of the study in any of the cohorts. These data indicate that although virtually all normal B-cells express CD22, only a subset seems to be affected by treatment with E-mab. In addition, the effect is maximal in this model at a dose of 300 mg/m². The reasons and possible clinical implications for this apparently distinctive activity of E-mab on certain B-cell subsets are currently being investigated.

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ACCESSION NUMBER: 2003:335988 BIOSIS
DOCUMENT NUMBER: PREV200300335988

TITLE: Phase I/II Trial of Epratuzumab (Humanized Anti-CD22 Antibody) in Non-Hodgkin's Lymphoma (NHL).

AUTHOR(S): Leonard, John P. [Reprint Author]; Coleman, Morton [Reprint Author]; Matthews, Jamie C. [Reprint Author]; Chadburn, Amy [Reprint Author]; Wegener, William A. [Reprint Author]; Hansen, Hans J. [Reprint Author]; Ziccardi, Heather [Reprint Author]; Kapushoc, Heather [Reprint Author]; Gayko, Urte [Reprint Author]; Cesano, Alessandra [Reprint Author]; Fields, Scott Z. [Reprint Author]; Goldenberg, David M. [Reprint Author]

CORPORATE SOURCE: Center for Lymphoma and Myeloma and Division of Hematology and Oncology, Weill Medical College of Cornell University and New York Presbyterian Hospital, New York, NY, USA

SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 1388. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.

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Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

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AB Epratuzumab (E-mab) is an unconjugated, **humanized IgG1** monoclonal antibody against the B-cell CD22 antigen (a sialoglycoprotein present on the cell surface of mature B-cells that is rapidly internalized upon binding of ligand or antibody), and is being developed for the treatment of NHL. We report extended follow up results from a single-center phase I/II trial examining the safety, efficacy and pharmacokinetics of E-mab in patients (pts) with relapsed/refractory NHL. E-mab was administered at escalating doses from 120 to 1000 mg/m² as an intravenous infusion once weekly for 4 treatments. Between April 1998 and September 2001, 114 pts were enrolled and 111 received gtoreq1 dose of study **drug** (median age 61 years; range 19 to 88 years). Approximately half had lesions of gtoreq5 cm, half had elevated lactate dehydrogenase (LDH) levels, and half had received gtoreq4 prior regimens, all of which are poor prognostic features. Overall, epratuzumab was well tolerated and no dose-limiting toxicity was observed. E-mab transiently decreased B-cell but not T-cell counts. No effect on immunoglobulin levels was observed. Due to the favorable infusion-related safety profile, 95% of infusions were completed in approximately 1 hour. The mean serum half-life of E-mab was 23 days. Among 51 indolent NHL pts evaluable for response across all dose levels (including level 1) and

histologies, 20 (39%) had stable disease and 9 (17.6%) had objective responses (3 complete responses or CR, 6 partial responses or PR). Of 52 evaluable aggressive NHL pts, 12 had stable disease (23%) and 5 (10%) objective responses were noted (3 CR, 2 PR). All clinical responses were observed at the 240-600 mg/m²/week levels, and in the follicular NHL and diffuse large B-cell (DLBCL) histologies only. Six of 14 (43%) and 3/11 (27%) of follicular pts treated at 360 mg/m²/week or 480 mg/m²/week, respectively, had objective responses. Median duration of response for this group was 47+ (11 to 99+) weeks, and median time to progression was 103+ (35 to 107+) weeks by Kaplan-Meier estimate. For the aggressive NHL responders, median duration of response was 38+ (13 to 38+) weeks and median time to progression was 35+ (23 to 35+) weeks. Responders had lower tumor burden, fewer prior therapies, and normal LDH compared with non-responders. Notably, however, the DLBCL responders had a median of 5 prior regimens (range 3-8), and included pts who relapsed after high dose chemotherapy and autologous stem cell transplant (3 pts) or were 80+ years old (1 pt) and therefore ineligible to receive high dose chemotherapy. Overall, 5 pts continue to be followed in response, with a median follow time of 2.3 years (range 1.4-3.9). In summary, E-mab therapy was well tolerated in pts with relapsed/refractory NHL at doses up to 1000 mg/m²/week (x 4), and produced clinical activity including durable complete responses in pts with follicular or diffuse large B-cell histologies. Ongoing and future studies are evaluating the optimal settings for use of this agent in NHL, including the determination of response rates in subsets of follicular and DLBCL pts (where clinical activity appears to be higher), confirmation of optimal dosing levels, and combination with other agents including rituximab and chemotherapy.

L28 ANSWER 21 OF 30 MEDLINE on STN
 ACCESSION NUMBER: 2001682592 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11728231
 TITLE: Antibody targeted therapeutics for lymphoma: new focus on the CD22 antigen and RNA.
 AUTHOR: Newton D L; Ryback S M
 CORPORATE SOURCE: SAIC Frederick and Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD 21702, USA.
 CONTRACT NUMBER: N01-CO-56000 (NCI)
 SOURCE: Expert opinion on biological therapy, (2001 Nov) 1 (6) 995-1003. Ref: 100
 Journal code: 101125414. ISSN: 1471-2598.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, ACADEMIC)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200208
 ENTRY DATE: Entered STN: 20011203
 Last Updated on STN: 20020821
 Entered Medline: 20020820
 AB The approval of antibodies for cancer treatment has provoked increased interest in the development of new and improved antibody-mediated therapies. This emerging approach centres on targeting CD22 on human B-cells with a monoclonal antibody (mAb). Anti-CD22 antibodies conjugated to a cytotoxic RNase elicits potent and specific killing of the lymphoma cells in vitro and in human lymphoma models in severe combined immune deficiency (SCID) mice. RNA damage caused by RNases could be an important alternative to

standard DNA damaging chemotherapeutics. Moreover, targeted RNases may overcome problems of toxicity and immunogenicity associated with plant- or bacterial toxin-containing immunotoxins.

L28 ANSWER 22 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:220142 BIOSIS
 DOCUMENT NUMBER: PREV200200220142
 TITLE: Durable response to 90-Yttrium-Epratuzumab (hLL2) in B-cell lymphoma failing chemotherapy by using dose-fractionation schedule.
 AUTHOR(S): Linden, Ola [Reprint author]; Tennvall, Jan [Reprint author]; Cavallin-Stahl, Eva [Reprint author]; Darte, Lennart; Ohlsson, Tomas; Hindorf, Cecilia; Wingardh, Karin; Strand, Sven-Erik
 CORPORATE SOURCE: Dept of Oncology, Lund University Hospital, Lund, Sweden
 SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 602a. print.
 Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
 CODEN: BLOOAW. ISSN: 0006-4971.
 DOCUMENT TYPE: Conference; (Meeting)
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 Conference; (Meeting Poster)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 3 Apr 2002
 Last Updated on STN: 3 Apr 2002

AB The humanized anti-CD22 antibody, Epratuzumab (hLL2, Immunomedics, Inc., Morris Plains, NJ) can be given repeatedly with no or minimal risk for neutralising Ab, making fractionated treatment with 90Y labeled hLL2 feasible. Patients (pts) with B-cell lymphoma relapsing or resistant to standard chemotherapy were treated in cohorts of 3-6 pts with increasing number (2-4) of weekly infusions of 90Y-hLL2. Pts with various subtypes of B-cell lymphoma; (transformed n=5; diffuse large B-cell n=5; follicular grade II n=4; mantle cell n=2; MALT n=1; B-CLL n=1) received either 5mCi/m²/infusion (group A), or 2.5mCi/m²/infusion (group B) if they had a history of prior high-dose chemotherapy with stem cell rescue. The first infusion for all pts also included 4 mCi of 111Indium for a scintigraphic verification of tumor targeting. A total amount of 1.5 mg/kg hLL2 was administered with each infusion. This treatment could be repeated once after 3 months (m), provided there was neither severe toxicity nor progression of disease. Thus far, 18 pts are enrolled: 13 in group A and 5 in B. In group A, the first 2 cohorts, treated with two and three weekly infusions respectively, included 3 pts each, and no dose-limiting toxicity (DLT) was seen. Of five patients in the third level (4 weekly infusions) there were two pts with dose-limiting hematological toxicity, both recently treated with cytosar 3g/m² before radioimmunotherapy. Accrual continues at the second level (3 infusions). Of 12 evaluable patients in group A, seven exhibited objective response. The event-free survival was (18m+, 17m+, 17m+ 5.5m+) for pts in CR/CRu and for pats showing PR (3.5m, 7m, 3m+). In this group (A) three of four follicular lymphoma responded (1CR, 2 PR) one of two diffuse large cell (1 CR), one of two mantle cell (1 CR) and one of two transformed as well as the only MALT lymphoma (CRu). In the low dose group (B), no DLT nor any response have been seen in the first five pats. Six of eight pats with CD22 positive tumor, whereas one of nine pats with weakly positive, negative or unknown CD22 expression, as measured by flow cytometry, exhibited response. Five pats have been retreated after 3 months without any DLT. Radioimmunotherapy of B-cell lymphoma employing

repeated weekly infusions with radiolabeled hLL2 (5mCi 90Y/m2) can result in durable objective remission in patients with various subtypes of lymphoma, who have failed prior chemotherapy. Three weekly infusions 5mCi/m2 can safely be administered with only minor hematological toxicity.

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ACCESSION NUMBER: 2002:129876 BIOSIS

DOCUMENT NUMBER: PREV200200129876

TITLE: Antitumour activity of Calicheamicin theta, Doxorubicin and anti-CD19 immunoconjugates in a human pre-B ALL cell line.

AUTHOR(S): Jendreyko, Nina [Reprint author]; Bernt, Kathrin [Reprint author]; Gaedcke, Gerhard [Reprint author]; Wrasidlo, Wolfgang [Reprint author]; Beutler, Ernest

CORPORATE SOURCE: Dept. of Pediatrics, Charite, Humboldt University, Berlin, Germany

SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 105a. print.

Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.

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DOCUMENT TYPE: Conference; (Meeting)

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AB Children with high risk ALL face a dismal prognosis, despite novel and extended conventional chemotherapy. Using cytotoxic assays we determined whether targeting the cytotoxic agents Calicheamicin theta and Doxorubicin to anti-CD19, which is highly expressed by B-cell leukemic blasts, might offer an effective therapeutic strategy. Also evaluated were anti-CD20 and anti-CD22 antibody conjugates. For comparison we included other anticancer drugs like Etoposide, Paclitaxel, Melphalan, Vinblastin, Camptothecan, Metothrexate and Genistein with different cytotoxic targets and mechanisms of drug action. The NALM6 cell line, derived from ALL cells with a HLA-DR+, CD19+ and CD10+ phenotype was used, because it causes disseminated and fatal leukemia in SCID mice and thus represents a clinical relevant model cell line for ALL. Calicheamicin theta was rationally designed on the basis of the natural product Calicheamicin gamma, and belongs to a group of naturally occurring enediyne, that binds in a sequence specific manner (TCCT) to the minor groove of DNA and induces double strand DNA breaks that ultimately induces apoptotic cell death. The cytotoxicity assays revealed that the most potent cytotoxic agent is Calicheamicin theta, with an IC₅₀ of 50fM. The cytotoxicity of a anti-CD19 immunoconjugate was 200fM, a value less than one order of magnitude below that of the free drug, and nearly three orders of magnitude higher than an immunoconjugate made from Doxorubicin and anti-CD19 mAb, with an IC₅₀ of 1nM. The three immunoconjugates of Doxorubicin made from anti-CD19, -20 and -22 gave nearly identical IC₅₀ values in the nanomolar range and their combined exposure to NALM6 cells also gave similar values. Thus using an "antibody cocktail" on this cell line provided no synergistic effect. The free unconjugated antibodies either singly or in combination showed no cytotoxicity within the concentration range investigated in our study (10⁻⁴ to 10⁻¹⁵) on this cell line neither with nor without the presence of complement. By far the most promising candidate for further preclinical studies of pediatric ALL

tumor targeting was observed in all diagnostic as well as posttherapeutic scans of all patients. In myeloablative therapies, the therapeutic activities were calculated based on the diagnostic radiation dosimetry, aiming at lung and kidney doses \leq 20Gy. Stem cells were reinfused when the whole-body activity retention fell below 20 mCi. In eight assessable patients, five had complete remissions, two experienced partial remissions (corresponding to an overall response rate of 87%), and one (low-dose) patient had progressive disease despite therapy. In the five assessable, actually stem-cell grafted patients, the complete response rate was 100%. Both CD20 and CD22 seem to be suitable target molecules for high-dose RAIT in a broad spectrum of hematological malignancies of B cell origin with a broad range of maturation stages (from acute lymphatic leukemia to Waldenstrom's macroglobulinemia). The better therapeutic outcome of patients undergoing high-dose, myeloablative RAIT favors this treatment concept over conventional, low-dose regimens.

L28 ANSWER 25 OF 30 MEDLINE on STN DUPLICATE 7
 ACCESSION NUMBER: 2000007390 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10541377
 TITLE: Radioimmunotherapy using ^{131}I -labeled anti-CD22 monoclonal antibody (LL2) in patients with previously treated B-cell lymphomas.
 AUTHOR: Linden O; Tennvall J; Cavallin-Stahl E; Darte L; Garkavij M; Lindner K J; Ljungberg M; Ohlsson T; Sjogreen K; Wingardh K; Strand S E
 CORPORATE SOURCE: Department of Oncology, Lund University Hospital, Sweden..
 ola.linden@onk.lu.se
 SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (1999 Oct) 5 (10 Suppl) 3287s-3291s.
 Journal code: 9502500. ISSN: 1078-0432.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
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 ENTRY MONTH: 199911
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 Entered Medline: 19991124

AB Experience in using rapidly internalizing antibodies, such as the anti-CD22 antibody, for radioimmunotherapy of B-cell lymphomas is still limited. The present study was conducted to assess the efficacy and toxicity of a ^{131}I -labeled anti-CD22 monoclonal antibody (mAb), LL2, in patients with B-cell lymphomas failing first- or second-line chemotherapy. Eligible patients were required to have measurable disease, less than 25% B cells in unseparated bone marrow, and an uptake of ^{99}mTc -labeled LL2Fab' in at least one lymphoma lesion on immunoscintigram. Eight of nine patients examined with immunoscintigraphy were unequivocally found to have an uptake, and therapy with ^{131}I -labeled anti-CD22 [$1330 \text{ MBq}/\text{m}^2$ ($36 \text{ mCi}/\text{m}^2$)] preceded by 20 mg of naked anti-CD22 mAb was administered. Three patients achieved partial remission (duration, 12, 3, and 2 months), and one patient with progressive lymphoma showed stable disease for 17 months. Four patients exhibited progressive disease. The toxicity was hematological. Patients with subnormal counts of neutrophils or platelets before therapy seemed to be more at risk for hematological side effects. Radioimmunotherapy in patients with B-cell lymphomas using ^{131}I -labeled mouse anti-CD22 can induce objective remission in patients with aggressive as well as indolent lymphomas who have failed prior chemotherapy.